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# Resistance exercise and vascular function: Training and obesity-related effects

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Resistance exercise and vascular function:  
Training and obesity-related effects

A dissertation submitted in partial fulfillment of the requirements for the degree of  
Doctor of Philosophy at Virginia Commonwealth University.

by

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# RESISTANCE TRAINING AND VASCULAR FUNCTION: TRAINING AND OBESITY-RELATED EFFECTS

By Grayson Lipford PhD.

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Endothelial dysfunction, or the inability of an artery to dilate sufficiently when subjected to excessive shear stress, serves both as a predictor of future cardiovascular events as well as an early indication of atherosclerosis. Several chronic disease states, including obesity, have been shown to alter endothelial function, which may be mediated through circulating pro- and anti-inflammatory adipokines. Still, the mechanisms by which obesity-related low-grade inflammation alters endothelial function are not fully elucidated. Acute and chronic endurance exercise training has previously been shown to be effective in improving endothelial function; however, chronic resistance exercise training is not universally regarded as beneficial to vascular functioning. Far fewer studies have examined the effect of acute resistance exercise on vascular function and adipokine release. To further understand the effects of resistance exercise training on vascular function, a meta-analysis was completed to examine the effects of resistance training on brachial artery flow mediated dilation (FMD), a common measure of endothelial function. The results of the meta-analysis indicate that resistance training has a small positive effect on FMD. Additionally, the effects of an acute bout of lower body resistance exercise on forearm blood flow (FBF) and two inflammatory cytokines were evaluated in obese ( $>30\%$  body fat) and non-obese ( $\leq 30\%$  body fat) subjects. It was hypothesized that the resistance exercise bout would increase FBF, that those changes would be greater in obese versus non-obese subjects, and that the changes in circulating cytokines (adiponectin and tumor necrosis factor- $\alpha$ ) would be related to changes in FBF. The results indicate that FBF measures in obese and non-obese subjects react in a divergent pattern immediately following resistance exercise but return to baseline within 24 hours. These changes were not related to changes in adiponectin or TNF- $\alpha$  although changes in adiponectin were related to changes in TNF- $\alpha$ . In conclusion, resistance exercise training programs may have a small positive effect on vascular function which may reduce overall cardiovascular disease risk. Additionally, obese and non-obese subjects display differing patterns of vascular responses to an acute bout of resistance exercise, supporting the view that obesity, and its associated low-grade inflammatory response, may negatively alter vascular homeostasis.

## INTRODUCTION

The vascular endothelium is the primary control tissue for vasomotor tone. Increases in blood velocity increase shear stress on the walls of vessels. The endothelium, a single layer of cells lining the walls of arteries, responds by releasing various vasodilators, most predominantly nitric oxide, into the smooth muscle surrounding the vessel. This causes smooth muscle relaxation, an increase in the diameter of the lumen and a decrease in blood velocity and shear stress. Proper endothelial function is a vital component of a healthy vasculature. Endothelial dysfunction, or the inability of an artery to dilate sufficiently when subjected to excessive shear stress, serves both as a predictor of future cardiovascular events as well as an early indication of atherosclerosis. (A. L. Huang et al., 2007; Perticone et al., 2001). The reaction of the vascular endothelium to shear stress heavily influences the degree of vasodilation that occurs in response to increases in blood flow (Furchgott & Zawadzki, 1980). Endothelial dysfunction is shown to be an early indicator of the progression of atherosclerosis with losses in vasodilation occurring before any clinical symptoms are present

Both acute and chronic endurance exercise training have previously been shown to be effective in improving endothelial function (Hambrecht et al., 1998; Kingwell, Tran, Cameron, Jennings, & Dart, 1996). Resistance exercise, however, is not universally regarded as beneficial to vascular functioning, with some training studies demonstrating

improvements (Anton et al., 2006; Copeland et al., 1996; Watts et al., 2004; Woo et al., 2004) and others demonstrating reductions in endothelial function (Cortez-Cooper et al., 2005). Despite these conflicting results, a common belief that resistance training decreases endothelial functioning has been generated in the scientific literature. We approached this question using a meta-analysis technique to examine the effect of resistance training on flow mediated dilation. We found that rather than decreasing endothelial function, resistance training increased flow-mediated dilation.

Few studies have examined acute resistance exercise (RE), however, and the results vary depending upon training status and method of measurement (Fahs, Heffernan, & Fernhall, 2009; Fernandez et al., 2010; Varady, Bhutani, Church, & Phillips, 2009). Also, few RE studies have used overweight or obese subjects. Rates of obesity in the western hemisphere have been increasing at an alarming rate over the last 40 years and it is associated with a variety of cardiovascular risk factors such as atherosclerosis, insulin resistance, type 2 diabetes, dyslipidemia and hypertension (Brook, 2006; Govindarajan, 2008). Obesity is also related to endothelial dysfunction (Williams et al., 2005). Body fat percentage, body mass index (BMI), and waist circumference independently relate to cardiovascular risk factors such as blood pressure, pulse wave velocity, and intima-media thickness (Williams et al., 2005). Additionally, increases in obesity activate the renin-angiotensin cascade, increase sympathetic tone (Govindarajan, 2008), and are associated with leptin (Hickey & Calsbeek, 2001) and insulin resistance (Yki-Jarvinen, 2003), all of which negatively affect vascular function.

Obese subjects also have elevated levels of pro-inflammatory cytokines. Inflammatory cytokines increase adhesion molecule activity thereby causing greater

monocyte adhesion and migration into artery walls where they consume LDL cholesterol and become foam cells, the building blocks of atherosclerotic lesions (K. K. Koh et al., 2005). Some cytokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), C-reactive protein, and interleukin-6 are pro-inflammatory while adiponectin, which is lower in obese subjects, is anti-inflammatory. Adiponectin increases nitric oxide availability, increases insulin sensitivity and blocks synthesis of TNF- $\alpha$ . (H. Chen, Montagnani, Funahashi, Shimomura, & Quon, 2003). Additionally, adiponectin has been shown to inhibit the pro-inflammatory effects of TNF- $\alpha$  as well as its synthesis (Ye, Gao, Yin, & He, 2007; C. Kobashi et al., 2005; Matsuzawa, Funahashi, Kihara, & Shimomura, 2004).

The effects of RE on levels of adiponectin are not well known (K. K. Koh, Han, & Quon, 2005). One study demonstrated increases in adiponectin in subjects who were trained weight lifters, but not in runners or sedentary lean subjects (Varady et al., 2009). The effects of RE on TNF- $\alpha$  are mixed with studies showing increases (Nieman et al., 2004), decreases (Phillips et al., 2008; Y. Tsai et al., 2006) or no change (Uchida et al., 2009) in TNF- $\alpha$ . Adiponectin can suppress TNF- $\alpha$ , so we hypothesized that adiponectin would increase, TNF- $\alpha$  would decrease and that the changes in each would be related to each other and to FBF. We found that while the changes in adiponectin and TNF- $\alpha$  after RE were related, they did not significantly change over time. However, adiponectin and TNF- $\alpha$  did correlate with measures of obesity, with adiponectin decreasing and TNF- $\alpha$  increasing as obesity increases.

Acute endurance exercise and exercise training have been shown to increase endothelial function. Few exercise studies, however have used resistance exercise as an intervention and few have used obese subjects, so the effects of resistance exercise on the

endothelial function of obese versus lean individuals is unknown. Systemic inflammation, which is more prevalent obese individuals, causes vascular dysfunction. A number of cytokines regulate inflammation; adiponectin and TNF- $\alpha$  are two cytokines that have significant effects. Considering the differences in levels of inflammatory cytokines between obese and non-obese subjects, evaluation of the mechanism by which inflammation affects the response of the endothelium to resistance exercise is warranted. Obesity is strongly correlated with both higher levels of TNF-  $\alpha$  and lower levels of adiponectin as well as endothelial dysfunction.

## **Literature Review**

### **Introduction**

Over 50 years ago, the Framingham study identified several risk factors for cardiovascular events, including elevated lipid levels, elevated blood pressure, excess body weight, lack of physical activity, smoking, low vital capacity, gout and diabetes (Dawber & Kannel, 1966). Since that time, investigators have searched for improved markers of cardiovascular health and disease risk and predictors of adverse cardiovascular events. A recent focus of this effort has been to further understand the mechanisms contributing to altered vascular function subsequent to changes in the vascular endothelium and circulating inflammatory cytokines.

Reactive hyperemia is the increased presence of blood in an area after restoration of blood flow following a decreased supply (Venes, 2005). This can occur during sustained muscular contractions which occlude blood flow or after supra-systolic pressure is applied to arteries supplying oxygenated blood to peripheral tissue, such as placing an inflated blood pressure cuff on an upper arm or thigh to restrict blood from flowing into the forearm or calf, respectively. When flow is restored by cessation of contraction or reduction in cuff pressure, shear stress on the vessel wall increases as blood quickly rushes through the previously flow-restricted artery. The vessel wall, particularly the vascular endothelium, works to relieve the shear stress by synthesizing substances, primarily nitric oxide, which cause the smooth muscle surrounding the lumen to relax and

the vessel to dilate (Joannides, Bellien, & Thuillez, 2006). This increase in lumen diameter reduces the speed of blood through the artery reducing shear stress. If the vessel is unable to adequately dilate, the shear stress may cause damage to the arterial wall which would increase the likelihood of plaque formation leading to atherosclerosis. The ability of a vessel to dilate is an indicator of the functional abilities of that vessel. Thus measures of forearm blood flow have become an accepted means of measuring vascular reactivity of arteries of the peripheral circulation during reactive hyperemia.

Proper endothelial function is a vital component of a healthy vasculature. Endothelial dysfunction, or the inability of an artery to dilate sufficiently when subjected to excessive shear stress, serves both as a predictor of future cardiovascular events as well as an early indication of atherosclerosis. (Huang et al., 2007; Perticone et al., 2001). The reaction of the vascular endothelium to shear stress heavily influences the degree of vasodilation that occurs in response to increases in blood flow (Furchgott & Zawadzki, 1980). Several disease states, however, affect the functioning of the endothelium. In particular, obesity has been shown to contribute to endothelial dysfunction and is associated with atherosclerosis, insulin resistance, type 2 diabetes, dyslipidemia, and hypertension (Brook, 2006; Govindarajan, Alpert, & Teiwani, 2008), each of which also negatively affects endothelial function.

Exercise, particularly endurance exercise training, has been shown to improve endothelial function, but research on the effects of resistance training is less common. For the purposes of this review, endurance exercise refers to rhythmic exercise utilizing large muscle groups with the intent to increase  $\text{VO}_2$ , while resistance exercise refers to exercise involving a few (1-15) short, near maximal muscular actions designed to stress

the contractile structure of muscle tissue. Additionally, acute exercise refers to a single bout of exercise while exercise training refers to a continuing program of exercise designed to improve fitness, either aerobically, in the case of endurance exercise training, or strength, in the case of resistance exercise training. Acute endurance exercise and endurance training have been demonstrated as effective in increasing measures of endothelial function (Hambrecht et al., 1998; Kingwell et al., 1996). Endurance exercise also affects levels of pro-inflammatory cytokines, which may explain some mechanisms of improved endothelial function that have been documented in response to endurance exercise training (Stewart et al., 2007; Fatouros et al., 2005; White, Castellano, & McCoy, 2006; Kohut et al., 2006). Adiponectin is an anti-inflammatory cytokine which may improve endothelial functioning (Eringa et al., 2007). It is produced by white adipocytes and is the most abundant cytokine found in plasma, but, paradoxically, as adipose tissue mass increases, adiponectin tends to decrease (Knudson, Dick, & Tune, 2007). Adiponectin is increased by endurance exercise training (Kim et al., 2007) which may contribute to the improvement in vascular function following a training program.

Conversely, resistance exercise training is not universally regarded as beneficial to vascular functioning. Chronic resistance training has been shown to increase forearm blood flow (Maiorana et al., 2000; Selig, 2004) and other measures of endothelial function (Watts et al., 2004; Woo et al., 2004) though there are concerns that it may have a negative effect on conduit artery function (Bertovic, 1999; Otsuki, 2006) due to the high blood pressures experienced during heavy resistance exercise (MacDougall, Tuxen, Sale, Moroz, & Sutton, 1985). Acute resistance exercise is not well studied. Varaday et al. demonstrated improvements in flow mediated dilation following a lower body



resistance exercise bout, but only in trained individuals (2010). Varaday et al. also only examined the acute effects immediately post-exercise. No study has examined forearm blood flow following an acute bout of resistance exercise involving lower body musculature nor studied the effects of resistance exercise on blood flow 24 hours post-exercise. Varaday et al. (2010) also demonstrated increases in adiponectin in resistance trained, non-obese subjects after resistance exercise and others have shown increases after resistance training (Fatouros et al., 2005), however, the effect of the increases in adiponectin on TNF- $\alpha$  and vascular reactivity, as assessed via strain-gauge plethysmography, after resistance exercise has not been investigated.

### **Anatomy and Physiology of the Artery**

Arterial vasculature is a branching pattern of vessels from large conduit arteries to arterioles to capillaries. Arteries are composed of three distinct layers. From the lumen outward, the layers consist of the tunica intima, tunica media, and the tunica externa or adventitia. The tunica intima is a single layer of cells called the endothelium, the tunica media consists of one or more layers of smooth muscle tissue and elastic connective tissue while the tunica externa is composed of fibrous connective tissue (Venes, 2005). The control mechanisms of the vessels vary with smaller vessels tending to be more responsive to pressure and metabolites while larger conduit arteries are more responsive to the shear stress generated by blood flow (Laughlin et al., 1995).

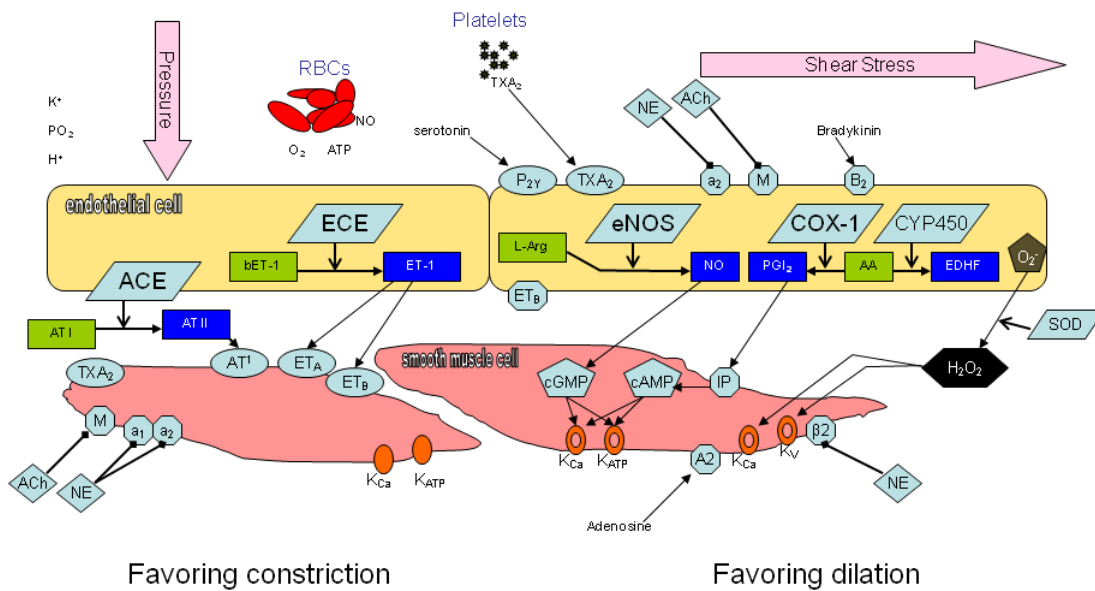
Large arteries withstand shear stresses in the range of 10-40 dynes/cm<sup>2</sup> (Resnick et al., 2003) as well as pressure forces acting perpendicular to the walls of the artery. At sites of curvature or bifurcation, the laminar shear forces are disrupted and flow becomes more turbulent (Berk, Abe, Min, Surapisitchat, & Yan, 2001). In healthy vessels,

endothelial cells synthesize and release nitric oxide in response to shear stress, but not in response to turbulent flow.

The endothelium is the primary control system for vascular tone. Furchott and Zawadzki observed that in preparations of rabbit thoracic aorta, when arterial rings were rubbed to remove endothelial cells, the smooth muscle no longer relaxed in response to a dose of acetylcholine (1980). Typically, in response to a stimulus, the endothelium releases nitric oxide which diffuses to the smooth muscle and causes relaxation.

Nitric oxide production is stimulated by acetylcholine (Furchgott & Zawadzki, 1980) via muscarinic receptor (Laughlin et al., 1995; Nishiyama et al., 2007) and by shear stress caused by the flow of blood parallel to the intima of the vessel (Nishiyama et al., 2007). Nitric oxide is also stimulated by bradykinin via a kinin receptor, norepinephrine via an  $\alpha_2$ -adrenergic receptor, substance P, serotonin (Laughlin et al., 1995; Nishiyama et al., 2007), thrombin, adenosine triphosphate (released from red blood cells) (Mortensen, Gonzalez-Alonso, Damsgaard, Saltin, & Hellsten, 2007), adenosine diphosphate (ADP) (Rubeiro, et al., 2009) and histamine (Duncker & Bache, 2006). Nitric oxide is synthesized from L-arginine by phosphorylation of endothelial nitric oxide synthase due to the shear stress of blood on the endothelial cell membrane which causes an influx of calcium, an essential co-factor of nitric oxide synthase (Moncada & Higgs, 1993). The L-arginine is hydroxylated to N-hydroxy-L-arginine and then further oxidized to nitric oxide and l-citrulline (Heffernan et al., 2009; McAllister, 1995). Nitric oxide then diffuses both into the lumen and into the smooth muscle cells where it acts by stimulating soluble guanylate cyclase and induces cyclic guanosine 3',5'-monophosphate (K. S. Heffernan et al., 2009) which increases production of cyclic-guanosine

monophosphate from guanosine triphosphate which causes relaxation in the smooth muscle cell (Moncada & Higgs, 1993; Moyna et al., 2004) via activation of cGMP-dependent protein kinase G and the protein phosphorylation of potassium channels, lowered calcium levels and dephosphorylation of myosin light chains (Heffernan et al., 2009). Other vasodilators may include prostaglandin prostacyclin (PGI<sub>2</sub>) and an endothelial-derived hyperpolarizing factor (McAllister, 1995). See Figure 1 below.



(adapted from Duncker & Bache, 2006)

Figure 1- Mechanism of shear-stress mediated vasodilation

Nitric oxide also may inhibit vascular smooth muscle proliferation and adhesion of platelets and leukocytes to endothelial cells (Yki-Jarvinen, 2003). Production of nitric oxide is inhibited by N<sup>G</sup>-monomethyl-L-arginine, a methylated L-arginine analogue which has allowed researchers to study the effects of various stimuli outside of nitric oxide effects (Moncada & Higgs, 1993).

Prostacyclin activation requires higher intra-cellular calcium levels than nitric oxide synthase and causes smooth muscle relaxation via a cyclic AMP second messenger.

Prostacyclin is stimulated by shear stress, substance P, thrombin and bradykinin. When stimulated, prostacyclin is synthesized from prostaglandin H<sub>2</sub> via hydrolysis of arachidonic acid by cyclooxygenase-2 (COX-2). It also inhibits platelet aggregation (Rubeiro, et al. 2009). Endothelial-derived hyperpolarizing factor plays a part in vasorelaxation, though its exact nature and mechanism are still not completely elucidated. There is evidence that it is linked to calcium sensitive potassium ion channels (Mortensen et al., 2007).

Another potential vasorelaxer is endothelin-1. At low levels, endothelin-1 binds with endothelial B receptors and causes the release of relaxation factors, but at higher levels, endothelin-1 binds with endothelial A receptors on smooth muscle cells causing calcium influx and vasoconstriction (Ribeiro, et al. 2009). These vasodilators seem to operate with some redundancy, so that a decrease in the functioning of one may cause an increase in others to compensate, though the effects of each are not equal (Mortensen et al., 2007).

Nitric oxide seems to be the most powerful vasodilator, especially during exercise. Blockades of either prostacyclin or both prostacyclin and endothelial-derived hyperpolarizing factor, which can also cause vasodilation, do not cause significant changes to blood flow. However, lower blood flow, and the resulting low oxygen tension, cause a greater off loading of ATP from red blood cells which cause additional vasodilation by binding to endothelial P<sub>2</sub>y-purinergic receptors stimulating nitric oxide synthase (Mortensen et al., 2007).

This endothelial-mediated vasodilation is used by healthy arteries to diminish shear stress caused by increases in blood flow. As an example, in a study by Tronc, et al.

(1996), an arteriovenous fistula was constructed between the common carotid artery and the jugular vein in rabbits. Blood flow proximal to the fistula increased to 196.2 ml/min while flow in the contra-lateral artery was 29 ml/min. This would cause an almost 7 fold increase in shear stress (Prior, Lloyd, Yang, & Terjung, 2003). After 4 weeks, the diameter of the artery had increased to 4.64 mm versus 2.54 in the contra-lateral artery. Meanwhile, the section of artery distal to the fistula was reduced in diameter to 2.07 mm due to diminished shear stress (Tronc et al., 1996). The increase in diameter reduced shear stress values to levels similar to that of the contra-lateral artery demonstrating the effects of vasodilation on shear stress. A sub-group of rabbits were given L-NAME, a nitric oxide inhibitor, in drinking water which resulted in only a partial adaptation, suggesting that nitric oxide also has a role in vascular remodeling.

The vasodilator responses of twelve healthy subjects were measured stress using strain-gauge plethysmography at baseline or after infusion with  $\text{N}^{\text{G}}$ -monomethyl-L-arginine, a nitric oxide synthase inhibitor, in response to an ischemic. Infusion of  $\text{N}^{\text{G}}$ -monomethyl-L-arginine caused a decrease in resting forearm blood flow by 29% and an increased vascular resistance of 26%. It also produced a downward and rightward shift in the dose-response to acetylcholine, an endothelium-dependent agonist. Vascular resistance was 125% greater with administration of  $\text{N}^{\text{G}}$ -monomethyl-L-arginine. Following a five minute ischemic stress, the treatment produced a decrease in peak flow of 16-22.3% and an increase in resistance of 22.8%. This study indicates that nitric oxide is also an important tonic vasodilator (Tronc et al., 1996)

## **Methods of Assessing Vascular Function**

Several methods of measuring vascular function have been developed. Four of the most common methods include flow-mediated dilation of the brachial artery, carotid intima-media thickness, pulse wave velocity, and strain-gauge plethysmography. The first three techniques measure larger conduit arteries while plethysmography measures the functioning of smaller, resistance arteries. In all cases, measurements should be conducted at the same time of the day, to avoid diurnal variations, and in a fasted state to avoid changes in endothelial function due to postprandial lipemia and glycemia (Brook, 2006). Finally, female subjects should be measured during the same phase of the menstrual cycle as endothelial function may vary over the course of the cycle (Adkisson et al., 2010).

Kasprzak, Klosinska, and Drozd (2006) state that “quantitative coronary angiography after inter-arterial infusion of acetylcholine is a clinical gold standard for the assessment of endothelial function in coronary arteries.” However, such direct measurements in coronary arteries are invasive generally carry a larger risk to the subject compared with non-invasive measures. It should only be used if coronary angiography becomes clinically necessary. A catheter would be inserted and positioned in the coronary artery where various vaso-reactive substances, such as acetylcholine, bradykinin and nitroglycerine would be infused. Direct angiographic images are made to and used to produce measurements of coronary vasodilation or vasoconstriction (Anderson et al., 1999). This procedure takes several hours and carries the risk of myocardial infarction, stroke or death (Kasprzak Klosinska & Drozd, 2006).

Endothelial dysfunction is systemic, so that if the coronary arteries are affected, other arteries throughout the organism would be affected similarly (Esper et al., 2006).

Therefore, measurements of changes in other arteries should be similar to changes in the coronary arteries. Study of the brachial artery (and femoral artery in children) has become a common approach to assessing endothelial function less-invasively. In these studies, the brachial artery is scanned by ultrasonography. The ultra sound transducer is used in B mode to produce images of a ~10 cm longitudinal section of the brachial artery while the subject lies supine. A transducer with a frequency of at least 7.0 MHz is necessary and the artery measured should be between 2.5 and 5 mm in diameter, which is the case in 90% of brachial arteries in the adult population and the femoral artery in children (Patel & Celermajer, 2006). Vasodilation of the brachial artery is measured in response to an infusion of acetylcholine or bradykinin, which increase the production and secretion of nitric oxide. In a study by Anderson et al, (1995), measurements of brachial vasodilation and coronary vasodilation in response to a dose of acetylcholine were compared in subjects with endothelial dysfunction and those with normal endothelial function. A significant, though weak, correlation was found between percent change in brachial artery diameter and coronary artery diameter in response to infusion of acetylcholine ( $r = 0.36$ ,  $p = 0.01$ ) indicating that brachial artery dilation “...may become a useful surrogate in assessing...” endothelial function (Anderson et al., 1995). Takase et al. (1998) followed up this study by comparing brachial and coronary endothelial function. In this study, coronary artery flow was increased with an infusion of 20.0  $\mu\text{g}$  and 30.0  $\mu\text{g}$  adenosine triphosphate, a precursor of adenosine, while brachial blood flow was increased by inducing reactive hyperemia with an occlusion cuff inflated to 200 mmHg for five minutes. Endothelial dependent dilation in both arteries were significantly and closely correlated ( $r = 0.79$ ,  $p = <0.001$ ). In this case, both arteries

were stimulated by increased shear stress generated by increased blood flow (flow mediated dilation). This technique of using the brachial artery as a “window” into the coronary arteries avoids the invasive catheterization of the coronary arteries.

Additionally, the use of brachial occlusion to generate reactive hyperemia with ultrasound measurement avoids drug infusions which could cause damage to the vascular or nervous system or subsequent infection from the needle insertion.

Brachial artery ultrasound measurement, however, requires adherence to several controls to ensure valid interpretation. Because dilation is blunted following eating, especially meals which are high in fat, subjects should be fasted prior to testing. Also, females subject’s may experience differing responses depending upon the progress of the menstrual cycle, so care must be made to insure that female subjects are measured during the same point in their cycle (Patel et al., 2006). However, in a study by Sorensen et al. (1995), neither time of day, food intake, or period in the menstrual cycle increased day to day variability in measurements. Time of day may also influence dilation with morning measurements seemingly less than afternoon or evening (Kasprzak et al., 2006), though other researchers found no difference between tests done at 9 AM and 2 PM (ter Avest, Holewijn, Stalenhoef, deGraaf, 2005).

Brachial artery ultrasound following flow mediated dilation (FMD) is relatively reproducible with trained technicians. Differences in brachial diameter of 0.2 mm can be identified 67% of the time and differences of 0.1 mm can be identified 52% of the time using sham arteries with lumens between 2.8 and 4.4 mm (Sorensen et al., 1995). Sorensen et al state that multiple measures, both before and after treatments, should be used to increase accuracy but that changes of at least 1-2% in diameter would be



necessary under the best case scenario to be detectable (Sorensen et al., 1995).

Additionally, mean dilation values vary considerably ranging from -1.3 to 14% in subjects with coronary heart disease, 0.75-12% in subjects with diabetes and 0.2-19.2% in healthy subjects (Kasprzak et al., 2006).

Both lower arm and upper arm occlusion can be used to induce reactive hyperemia in the brachial artery with upper arm occlusion providing larger amounts of dilation but taking longer to peak. Finally, proper positioning of the calipers, which is typically done by visual inspection, requires a trained operator as the post occlusion diameter change is typically about 0.3 mm or less (Kaspizak et al., 2006).

There are concerns about inter-researcher and inter-individual variability of measurement. In a study performed by Sejda, Pitha, Svandova, Poledne (2005), two physicians conducted identical assessments on two days (a total of 4 measurements). The researchers found that two measurements made on consecutive days which were evaluated by the same physician did not significantly differ. However, when two different physicians evaluated measurements from the same day, the measures differed significantly. This may indicate that either only one physician should do the evaluation or that there is a large variability in individual endothelial function, and test procedures must be made identical to achieve valid results. Other researchers found no difference in two repeated measures at 9 AM or between measures at 9 AM and 2 PM, suggesting that the presence of two different assessors caused the variability in the study by Sejda et al. (ter Avest et al., 2005)

Intima-media thickness (IMT) is another frequently used measure of endothelial function. As inflammation occurs, more macrophages invade the media causing

thickening of the arterial wall due to accumulation of foam cells and smooth muscle cell proliferation. A thickening arterial wall may be an indicator of atherosclerosis development. Carotid arteries are frequently examined for thickening of the intima-media as they undergo the same level of atherosclerotic development as coronary arteries (Gullu et al., 2006). IMT is measured normally with ultrasonography using a 7.5 MHz linear-array. Both the common carotid and the internal carotid arteries may be examined. The subject is supine and a scan is made proximal to the carotid bifurcation. Measurements should be made multiple times at several sites to assure accurate data. Assessments of the carotid ultrasound images are then performed by researchers blinded to any clinical information. (O'Leary et al., 1999). Measurements of IMT are stable with consecutive tests and tests performed at different times of the day generate similar results (Sejda et al., 2005).

Carotid IMT is interrelated to FMD with one study finding a correlation ( $r = -0.388$ ,  $p < 0.01$ ) which indicated that as IMT increases, FMD decreases (Gullu et al., 2006). Trosheid et al (2005) did not find a significant correlation between IMT and PWV, however, indicating that the two measures may be evaluating different constructs of arterial structure.

A third measure of conduit artery endothelial function is pulse wave velocity (PWV). Blood ejected from the left ventricle creates a pressure wave that travels from the aorta and central arteries, such as the femoral and carotid to the peripheral arteries such as the brachial, radial and dorsal pedis arteries. This wave will be reflected from points along the vascular tree back towards the left ventricle. At the peripheral sites, the reflecting points are close, so the reflected wave adds to the systolic wave creating a

larger systolic pressure. At the central arteries, the wave must travel out to the reflecting points and then back to the heart. If the wave moves slowly out and back, then the reflected wave does not reach the heart until after left ventricular ejection has ended and central systolic pressure is not augmented, however, as arteries grow stiffer or hypertension develops, the pulse wave will move faster through the vascular system, returning as a reflection before the end of left ventricular ejection, thus amplifying the central pressure. This is why brachial systolic pressure and pulse pressure are greater than aortic systolic pressure and pulse pressure (Boutouyrie, 2008).

A number of organs, such as the heart, the kidneys and the brain are directly affected by an amplification of central pressure and these organs, along with the vasculature, may be more likely to become damaged, further increasing the development of atherosclerosis (Boutouyrie, 2008).

PWV can be assessed invasively through catheterization and then measured with a fluid filled catheter or from a microtip catheter. Non-invasively, PWV can be measured using applanation tonometry. This method involves applying pressure with a pressure sensor until the artery is flattened then the sensor measures the pressure against the flattened section. Because this works best when the vessel is flattened against a bone or other hard surface, using it on the carotid or brachial arteries is more difficult and corrections must be made for this fact, as well as to the hold down pressure applied to the sensor and the amount of amplification which occurs between the aorta and the carotid. Discussion of these corrections is beyond the scope of this paper. The amplification index is the ratio between the amplitude of the reflected wave and the pulse pressure (Boutouyrie, 2008).

Mercury-in silastic strain-gauge plethysmography is a method used to measure the function of limb resistance arteries. Blood flow is measured by recording changes in the diameter of a limb segment and calculating flow expressed in milliliters per minute per 100 milliliters of tissue (ml/min/100 ml). The typical method of measurement involves attaching a mercury-in-silastic strain-gauge to the largest part of the forearm and placing the forearm above the level of the heart. A fast-inflating occlusion cuff is placed around the upper arm and a smaller cuff is placed around the wrist and inflated to 50 mmHg to eliminate hand circulation from the measurements. The majority of hand circulation is through the skin and the hand contains a large number of arteriovenous shunts, thus “hand blood flow has different pharmacology and physiology from forearm blood flow.”(Benjamin et al., 1995). The upper arm cuffs are inflated to a pressure which inhibits venous outflow for 7-15 seconds then released for 7-15 seconds. During an occlusion period, the upper cuffs are inflated to a pressure which will stop arterial flow, typically ~250 mmHg, and this occlusion is maintained for 4.5-5 minutes. Data from the strain-gauges are recorded by computer and values of forearm blood flow (FBF) area under the curve are calculated using the trapezoid technique. Resistance to flow is calculated as mean arterial pressure divided by FBF. In many cases, baseline measurements are made followed by infusion of acetylcholine to measure endothelial-dependent dilation. This is followed by infusion of substances such as isosorbide dinitrate, which is an endothelium-independent vasodilator and these measures are used as a control. These are administered by inserting a catheter into the brachial artery. Blood pressure measurements can be made via the catheter using a pressure transducer as well (Higashi, Sasaki, Nakagawa, Matsuura, Kajiyama et al., 2001). There is some

concern about day to day variability in measurements but one time measurements are less troublesome (Anderson et al., 1999). A strong correlation exists between acetylcholine-mediated dilation and dilation in response to reactive hyperemia from vascular occlusion. Higashi et al. (2001) found an “almost identical” response to reactive hyperemia as to acetylcholine ( $r = 0.91$ ,  $p < 0.001$ ) even when subjects were separated into normal blood pressure and hypertensive groups. Plethysmography has also been used to study venous capacitance (Alomari, et al. 2004) though technical considerations should be taken into account to assure valid interpretation of results (Halliwill, 2004).

### **Predictive endothelial measures**

Measurements of endothelial function can effectively predict the risk of coronary incidents. These predictions can be performed by measuring vascular responsiveness at a peripheral artery and using that measurement as a proxy for coronary or other arteries. Huang et al. (2007) used flow mediated dilation of the brachial artery as a predictor of cardiovascular events in a study of patients with peripheral arterial disease and found that patients who experienced an event within a median time frame of 309 days had a lower FMD (4.5% vs. 6.9%) and lower hyperemic flow, 75 cm/s vs. 95 cm/s. Brevetti et al. (2003) examined 131 patients and followed them for an average of 23 months, recording cardiovascular events. The patients without a cardiovascular event during the follow up period had a mean flow mediated dilation of 7.6% while those who experienced a cardiovascular event had a mean of 5.8%.

Carotid IMT is a predictor of cardiovascular events as well. In a study of 444 patients over a mean of 24 months, survival rates of those with an IMT in the largest tertile ( $>0.71$  mm) were significantly lower than those in the lowest tertile ( $<0.62$ mm)

(Fathi, Haluska, Isbel, Short, & Marwick, 2004). In the study by Juonala et al. (2004) of young adults (24-39 years), IMT was correlated inversely with FMD of the brachial artery ( $p < 0.001$ ) when adjusted for age, sex, brachial vessel size and other risk variables establishing a link between carotid intima media thickness and endothelial function.

PWV also predicts increases in coronary heart disease. Patients who belonged to the first and second tertiles of the Framingham risk score had steeper increases in coronary heart disease and the area under the curve for carotid-femoral PWV decreased from the lowest to highest tertile (Boutouyrie, 2008).

Plethysmography has also been demonstrated to be predictive of cardiovascular events. In a study examining 198 patients with acute coronary syndromes, subjects who experienced a cardiovascular incident over a mean follow-up period of 48 months had a significantly reduced response to acetylcholine after adjustment for other risk factors (Fichtlscherer, Breuer, & Zeiher, 2004). Another study by Perticone et al. (2001) of 225 hypertensive patients found that the cardiovascular event rate for the first tertile (FBF increase of 30-184% in response to acetylcholine infusion) was 57.2% over a follow up period of 7 years while the third tertile (blood flow increase of 339-760%) was 14.4%, and the differences remained significant after exclusion of “soft” cardiovascular events and including only myocardial infarction and stroke. During an average 32 month follow up period, the number of events per 100 patient years ranged from 8.17 in the lowest blood flow tertile to 2.02 in the highest tertile, a significant difference even after accounting for other risk factors, including blood pressure.

There is an inconsistency in endothelial function studies with regard to the techniques used to measure endothelial function (Brook, 2006). This makes comparing

studies utilizing different methods or different techniques of the same method difficult. It is possible that different effects of a treatment on endothelial function may be seen with different measurement methods. For example, the change in resistance vessel function may be different than in conduit vessels and both may not completely match coronary endothelial function changes (Brook, 2006). Comparisons should be made with caution though any of the techniques are effective at indicating endothelial dysfunction.

### **Atherosclerosis and Heart Disease**

Endothelial dysfunction is an early warning indicator for atherosclerosis with losses in vasodilation occurring before there is any clinical symptoms present. Atherosclerosis, the largest cause of death in adults since the beginning of last century (Callow, 2002), is caused by infiltration of low density lipoprotein cholesterol across the endothelial wall where it becomes trapped and an inflammatory response is initiated. Early in its progression, endothelial cells become more permeable to lipoproteins and angiotensin II upregulates adhesion molecules on the endothelial cell membrane causing increased adhesion of leukocytes to the vessel wall. These macrophages migrate and engulf the low density lipoproteins. Mid-way in its progress, fatty streaks appear on the vessel wall. This is the accumulation of lipid laden macrophages, called foam cells. Platelets bind to the dysfunctional vessel wall, recruit monocytes and cause the proliferation of smooth muscle cells into the lesion. This has the effect of thickening the vessel wall and results in compensatory vessel dilation. Platelets also release thromboxane A<sub>2</sub> which is a facilitator of platelet aggregation, but also a vasoconstrictor (Khan, 2004). Finally, the cycle of recruitment and growth leads to formation of fibrous tissue and a continuing increase in the size of the plaque. A fibrous cap develops over the

plaque, becoming part of the vessel wall. Underneath this cap is a core of leukocytes, lipids and debris that may become necrotic. The fibrous cap may become unstable and rupture spilling the plaque contents into the blood stream, possibly forming a thrombus causing a cardiovascular event (Khan, 2004).

Endothelial function has been shown to be impaired in patients with atherosclerosis or with only risk factors for the disease. Since this impairment can occur before any thickening of the intima-media, endothelial dysfunction is an early manifestation of atherosclerosis. Impairment of endothelial function in subjects with atherosclerosis has been demonstrated in the resistance arteries via plethysmography as well as in conduit arteries using brachial ultrasound artery diameter measurement (Anderson, 1995). In a study by Ludmer et al. (1986) arteries with partial blockages did not respond to acetylcholine with vasodilatation, but rather with vasoconstriction, an abnormal response. Flow mediated dilation is a significant predictor of cardiovascular events in individuals with peripheral arterial disease. Researchers (Huang et al., 2007) measured brachial artery endothelial function using ultrasound two-dimensional and pulsed Doppler flow velocity signals just above the antecubital crease. Hyperemia was induced by inflating a blood pressure cuff to greater than 200 mm/hg for five minutes then releasing it. The measurements were made 60 seconds following cuff deflation and compared to brachial artery dilation following administration of nitroglycerin, which is not endothelium dependent. Patients in both studies with lower measures of reactive hyperemia were significantly more likely to experience a cardiovascular event in the following two to three years. In atherosclerotic coronary arteries, the dilation response to shear stress is blunted. Vita et al. (1989) compared coronary artery dilation in response to



shear stress in arteries with atherosclerosis to arteries without atherosclerosis. The atherosclerotic arteries did not dilate to the same percent as smooth arteries, thus they had to withstand more shear stress. The authors hypothesized that atherosclerosis causes a breakdown in the control mechanism of flow mediated dilation (Vita et al., 1989).

Another study hypothesized that impairment in flow-mediated dilation is progressive with different states of coronary artery disease. Zeiher et al. (1991) classified patients into four groups: 1) patients with normal, smooth coronary arteries and normal cholesterol levels, 2) patients with normal, smooth coronary arteries but with hypercholesterolemia, 3) patients with some coronary artery disease, but normal arterial walls where the measurements were taken and, 4) patients with coronary artery disease and stenosis of the artery being measured, the proximal left anterior descending artery. The authors found deterioration in endothelial function which worsened with advancing disease. Group 2 had an abnormal response to acetylcholine infusion, Group 3 had an abnormal response to both acetylcholine and a cold pressor test while Group 4 displayed abnormal responses to all stimuli. Increasing vascular disease causes an increasing impairment in endothelial function (Zeiher et al., 1991).

The thrombotic material in atherosclerotic lesions itself may also contain vasoconstrictive substances. Adlbrecht et al. (2007) removed thrombus material from subjects' hearts during acute myocardial infarction when the subjects had not received any anti-thrombotic therapy. The material removed contained a neutrophil/platelet/fibrin combination. Few of the samples contained atherosclerotic plaque materials such as foam cells, cholesterol clefts, smooth muscle cells or endothelial cells. The thrombi were homogenized and were administered to rings of porcine coronary artery *in vitro*. The

administration of the thrombi material caused a mean increase in vessel wall tension of 65.5% of maximal contractile capacity while administration of control plasma resulted in mean increases of only 11.1% of vasoconstriction. Additionally, the thrombus material administration-caused constriction did not abate until approximately one hour later while the constriction caused by control plasma subsided within 15 minutes. The authors noted that even the control plasma probably contained some amount of active vasoconstrictors which caused the negligible vasoconstriction. Additionally, administration of tezosentan, a thrombus endothelin receptor antagonist, inhibited coronary thrombus homogenate-induced vasoconstriction while the same administration to coronary arteries vasoconstricted with clotted whole blood from healthy subjects resulted in no change in vasoconstriction. This would indicate that thrombus endothelin (ET) is present in high concentrations in atherosclerotic plaque where activated neutrophils have been shown to release ET and is the major vasoconstrictor associated with coronary thrombi (Adlbrecht et al., 2007).

## **Obesity and Cardiovascular Disease**

*Mechanism of Effects.* Obesity is related to endothelial dysfunction (Williams et al., 2005). Obesity is also related to a variety of cardiovascular risk factors such as atherosclerosis, insulin resistance, type 2 diabetes, dyslipidemia, hypertension and endothelial dysfunction (Brook, 2006; Govindarajan et al., 2008). Separating the effects of obesity alone from the effects of these other factors on endothelial function is difficult. There are four specific conditions that are associated with obesity that contribute to endothelial dysfunction; 1) elevation in angiotensin two, 2) heightened nervous system tone, 3) leptin resistance, and 4) insulin resistance and type two diabetes.

First, the renin-angiotensin system, which is normally contributes to the regulation of body weight and plasma volume, is activated in obesity even when sodium and fluid volume are normal. Typically, renin is released from the kidney in response to low blood pressure due to low plasma volume. Renin acts upon angiotensinogen from the liver to form angiotensin I. Angiotensin I is converted by angiotensin converting enzyme from the lungs into angiotensin II. Angiotensin II may also promote cardiac hypertrophy, endothelial dysfunction, and increase tissue levels of reactive oxygen species (de Kloet, Krause, & Woods, 2010). The system also up regulates plasminogen activator inhibitor-1 which leads to decreased fibrin degradation and increases in coagulation, thrombus formation, and extra cellular matrix formation (Govindarajan et al., 2008). Weight loss has been shown to reduce renin activity in obese subjects (Govindarajan et al., 2008). Angiotensin II is also a powerful vasoconstrictor and stimulates (Hickey & Calsbeek, 2001) the adrenal cortex to release aldosterone which causes the kidneys to reabsorb more sodium and water increasing blood volume. There are three other mechanisms by which the system is activated in obesity, however. First, adipose tissue is itself a source of angiotensinogen leading to activation of the system. Secondly, a lipocyte-derived factor causes the liver to synthesize an increased amount of aldosterone. Finally, the resulting increase in renin levels may activate the sympathetic nervous system. Each of these may result in additional vasoconstriction (Govindarajan, 2008).

A second possible consequence of obesity is a heightened sympathetic nervous system tone, which has been observed in obese hypertensives more commonly than normal weight hypertensives. Sympathetic activation causes vasoconstriction, however,

a low sympathetic tone may play a part in the development of obesity as normal sympathetic tone may account for up to 5% of daily energy expenditure (Govindarajan et al., 2008).

Thirdly, increases in obesity are associated with leptin resistance. Leptin provides a feeling of fullness however, in leptin resistance this anti-starvation hormone ceases to provide the feeling of satiety, thus leading to overeating and additional weight gain. Leptin is synthesized by white adipose tissue and is found in high concentrations in obese subjects. Leptin may have a cardiovascular protective role but leptin resistance may cause these effects to be altered in ways that are not clear (Hickey & Calsbeek, 2001).

Finally, obesity is significantly related to insulin resistance and type II diabetes, which also involve hyperinsulinemia and the cardiometabolic syndrome. Insulin has two effects, a chronic and an acute effect. The acute effects regulate substrate metabolism while the chronic effects influence growth and proliferation. Insulin resistance is mainly due to the metabolic effects of insulin, however, whether insulin resistance down regulates the chronic effects, which include cell growth and extracellular matrix expansion, are unclear, but may cause vascular wall stiffening. Additionally, insulin resistance also causes an over-expression of proinflammatory cytokines, adhesion molecules and chemokines in addition to an increase in the production of reactive oxygen species due to increased glucose autooxidation and mitochondrial generation of superoxide. Insulin, when given intravenously, is a slow acting and weak acetylcholine-mediated vasodilator but insulin can activate the sympathetic nervous system, with resulting vasoconstriction countering acetylcholine mediated vasodilation. A state of insulin resistance may cause the insulin-mediated dilation to be diminished but treatments

that improve insulin sensitivity have also improved endothelial function (Yki-Jarvinen, 2003).

*Defining Obesity.* Exactly how obesity is defined is not agreed upon within this research field. Few researchers utilizing subject groups based upon measures of obesity define the selection criteria used aside from stating the mean BMI, weight, or body composition of the groups after selection. However, Higashi et al. (2001) used subjects with a BMI  $\leq 24$  for the lean group and  $\geq 27$  for the obese group. Van Guilder et al. (2008) used a similar criteria of subjects with a BMI  $\leq 25$  for the lean group and  $\geq 27$  for the obese group. One paper defined a single group of subjects as having “a healthy body fat” which equated to a body fat of 10-20% for males and 15-25% for females (Ferguson et al., 2004).

There is sparse research regarding disease risk, particularly vascular dysfunction, in relation to body composition expressed as percent body fat or fat-free mass. Calling et al. (2006) used body fat percentage, as determined by bioelectrical impedance, as a predictor of cardiovascular events in men and women of a mean age of approximately 58 years. Dividing the subjects into quartiles based on body fatness, male quartile 1 was 6-17% and served as the reference quartile. Quartiles 2-4 were 18-20, 21-23, and 23-54%. For women, quartiles 1-4 were 8-27, 28-30, 31-34, and 35-49% respectively. There was a significant trend for a higher number of cardiovascular incidents and cardiovascular deaths in males as body fat percentage increased. In females, as body fat percentage increased, there was a significant trend for increasing cardiovascular incidents and ischemic strokes. This was true even after controlling for age, smoking, alcohol intake, physical activity, height, diabetes, systolic blood pressure, use of blood pressure-lowering drugs and lipid-lowering drugs. No information regarding vascular function was

presented. However, in males, quartiles 2-4 presented mean BMI scores that fell into the overweight category and quartile 4 presented a mean waist circumference of 101 cm, just under the 102 cm risk factor level as determined by the Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults.,1998). Female quartile 3 mean BMI fell into the overweight range while quartile 4 fell into the obese range. Waist circumference in quartile 4 also fell into the risk category. In some cases, researchers found that percent fat remained a predictor when controlling for BMI, but in other cases, it did not (Calling et al., 2006).

Lee et al. (Lee, Blair, & Jackson, 1999) examined the role of cardiovascular fitness in males in conjunction with percent fat. The subjects were divided into three groups based upon their percent fat, using norm percentile scores of <25%, 25-75% and over 75%. The reasoning behind this classification system was not provided. However, as the groups' percent fat increased, so did the groups' mean BMI. The "lean group" was defined as those with percent fat <16.7%, and the fit and unfit groups' BMI in that category were 23.6 and 24.3. The "normal" group body fat range was 16.7 to <25% and the fit and unfit groups' BMI were 25.6 and 26.5. The obese group was defined as a fat percentage over 25% and the unfit and fit groups' BMI were 30.1 and 26.4. Since even the normal body fat and high body fat groups also had overweight or obese BMI scores, it would be premature to conclude that percent fat is a better or worse predictor than BMI. It would be more informative if subjects with different percent fat levels were matched

for BMI so the possibly confounding effects of BMI can be controlled. This study however, did also find that waist girth was a significant predictor of mortality.

Christou et al. (2005) examined relationships between cardiovascular risk factors, such as blood pressure, pulse wave velocity, and intima-media thickness and percent fat, BMI, and waist circumference. They found that although all three body fatness measures independently related to cardiovascular risk, no single measure was superior at predicting cardiovascular risk.

*Weight loss.* While obesity is closely associated with endothelial function, weight loss does not necessarily improve it. In studies involving only diet as a treatment, there is no overall improvement in endothelial function while studies that involve both diet and exercise show an improvement (Brook, 2006). However, most subjects in these studies have co-morbidities, so isolating the effects of weight loss is difficult. For example, a diet that causes weight loss may also cause a lowering of blood lipids. Improvements in endothelial function may be due to the weight loss, the change in lipids, a combination of both or an undetected factor. In most studies, there is not a clear relationship between the amount of weight lost and improvements in endothelial function (Brook, 2006). A further confounding factor is the variance in endothelial function within the obese population. Apovian et al. (2008) measured inflammation levels in adipose tissue in obese subjects and found the subjects with the greater local inflammation had significantly lower FMD as compared to the subjects without it (8.5% vs. 10.8%  $p < 0.05$ ). Additionally, subjects with higher inflammation had significantly greater levels of adipose CD68 and TNF- $\alpha$  gene expression. Also, plasma levels of CRP were higher and

adiponectin levels were lower. Although the effects of obesity itself are unknown, obesity is related to a variety of conditions which may worsen endothelial function.

### **The Inflammatory Response and Its Effects on the Endothelium**

At the initiation of inflammation at the endothelium, leukocytes in the blood will roll along the endothelium in the artery and bind to the arterial wall. E-selectin or P-selectin expressed on endothelial cell membranes will bind with mucins on the leukocyte resulting in a weak bond. Next, cell adhesion molecules, such as ICAM-1 and VCAM-1 bind with integrins (LFA-1, CD11a/CD18, CD11b/CD18 and MAC-1) located on the leukocyte membrane forming a strong adhesion. Chemokines change the integrins on leukocytes as well as cell adhesion molecules on endothelial cells, activating them, allowing stronger adhesion and attracting leukocytes to these areas of the vessel. Following adhesion, PECAMs mediate migration of the leukocyte between adjacent endothelial cells into the tissue where the leukocyte will ingest the bacteria or foreign matter, such as cholesterol and release additional chemokines, such as interleukin-8 (IL-8), to attract additional leukocytes. Chemokines signal leukocytes through receptors on the cell membrane and activate by way of G-proteins. Chemokines are produced by both leukocytes and endothelial cells.

*Inflammatory Markers and Endothelial Function.* Cytokines or other substances which increase vascular inflammation will increase adhesion molecule activity causing greater monocyte migration into artery walls. Monocytes become macrophages, consume oxidized low density lipoprotein and recruit more monocytes through chemokine release, eventually macrophages become lipid-laden foam cells (Koh et al., 2005). Over time, these cells die and spill their contents, further increasing macrophage recruitment. The



thickening artery wall loses the elasticity which normally absorbs the pulsatile forces of blood flow and leads to a reduced ability to dilate in response to increased shear stress caused by increases in blood flow.

Several cytokines affect the ability of the endothelium to synthesize nitric oxide, cause vasoconstriction or increase inflammation including adiponectin, angiotensinogen, C reactive protein (CRP), endothelin-1, interleukin-1 (IL-1), interleukin-6 (IL6), leptin, plasminogen activator inhibitor-1 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).

### *Angiotensinogen*

Angiotensinogen, mainly produced by the liver, is the precursor for angiotensin I and the angiotensin-renin cascade. Renin, produced in the kidneys converts angiotensinogen to angiotensin I which is then converted to angiotensin II by angiotensin converting enzyme from the lungs. Angiotensin II stimulates the zona glomerulosa to release aldosterone which increases sodium and water retention. White adipose tissue also produces angiotensinogen and, in obesity, levels are elevated. This leads to an over abundance of angiotensin-1, angiotensin-2 and aldosterone resulting in fluid retention and increased blood pressure. Additionally, angiotensinogen decreases the bioavailability of nitric oxide and increases ICAM-1, VCAM-1, and platelet adhesion. Combined with the increased risk of vascular injury due to high blood pressure, an increased risk of thrombus formation develops. Angiotensin II causes vasoconstriction and increases vessel wall permeability, monocyte and lymphocyte infiltration, phagocytic activity, and activates signaling pathways via NF- $\kappa$ B at two angiotensin II receptors (AT1 and AT2) that stimulate MCP-1, RANTES, chemokines, IL-6, VCAM-1, ICAM-1 and angiotensinogen. In addition, angiotensin II degrades into angiotensin III and IV causing

additional cardiovascular effects. (Ruiz-Ortega, Esteban, & Egido, 2007). Finally, increased circulating renin may stimulate the sympathetic nervous system leading to vasoconstriction (Govindarajan et al., 2008).

### *C-Reactive Protein*

CRP levels rise with obesity and diabetes and are reduced in weight loss. Suggested levels of CRP are < 1.0mg/L with 1.0-3.0 considered moderate and >3.0 considered high (Haffner, 2006). CRP is produced in the liver and may be synthesized in adipose tissue and is increased by IL-6 (Trayhurn, 2005; Blake & Ridker, 2001). CRP has been shown to directly inhibit arterial dilation (Annambhotla et al., 2008) and stimulates monocyte release of nitric oxide synthase, causing endothelial dysfunction. CRP levels greater than 6mg/L results in a 75% increase risk of restenosis during a five year follow up for individuals with cardiovascular disease versus subjects with values less than 1 mg/L and baseline CRP levels were higher in men who developed peripheral artery disease, however, physical activity and cardiorespiratory fitness are inversely related to CRP levels (Albert, Glynn, & Ridker, 2004; Plaisance et al., 2006).

### *Endothelin-1*

Endothelin-1 is synthesized mainly by endothelial cells, but also in nerve cells, renal cells, inflammatory and smooth muscle cells. Endothelial cells have two receptors for endothelin-1, an ET<sub>A</sub> receptor which promotes vasoconstriction, and an ET<sub>B</sub> receptor which promotes vasodilation. At low doses, endothelin-1 will cause vasodilation, but as the dose increases, it will cause vasoconstriction (Khan, 2004). In coronary arteries, however, there exists a two and a half times higher endothelin-1 mRNA expression compared with the aorta and ET<sub>A</sub> receptors are dominant, thus endothelin-1 acts mainly

as a vasoconstrictor in the heart (Thorin & Webb, 2010). Thus, endothelin-1 may be primarily responsible for coronary vascular tone.

#### *Interleukin-1*

IL-1 is increased in patients with coronary artery disease, especially unstable cases. IL-1 $\beta$  is released by macrophages within the vessel wall during the inflammatory response (Koh et al., 2005). It increases surface expression of VCAM-1, ICAM-1, e-selectin and p-selectin (Edwards et al., 2007). It also stimulates B cells and thymocytes to proliferate and mature and increases the secretion of IL-2 which activates and differentiates cytotoxic T-cells during an immune response (Venes, 2005).

#### *Interleukin-6*

IL-6 is expressed in, and released by, macrophages within the vessel wall during the inflammatory response and is the principle procoagulant cytokine secreted by adipocytes and all other multinucleated cells, including muscle cells (Koh et al., 2005). Adipose tissue also contributes a significant volume of IL-6 (Hutley & Prins, 2005). Levels are increased in obese subjects and those with insulin resistance (Trayhurn, 2005). IL-6 has been shown to inhibit insulin action in muscle, liver and adipose tissue (Hutley & Prins, 2005). IL-6 increases plasma concentrations of fibrinogen, plasminogen activator inhibitor-1 and CRP (Koh et al., 2005). It also increases expression of VCAM-1 and ICAM-1 (Edwards et al., 2007).

#### *Leptin*

Leptin is an adipokine which is normally found in plasma concentrations of 3-5 ng/ml in healthy subjects, but at levels as high as 90-95 ng/ml in obese subjects (Knudson, 2007). Leptin is upregulated by PPAR $\gamma$  ligands (Trayhurn, 2005).

Leptin has been termed an “anti-starvation” hormone, as decreases in leptin will lead to increases in appetite. However, the higher levels of leptin in obese subjects do not reduce appetite, thus suggesting a “leptin-resistance” in obesity (Hickey and Calsbeek, 2001). Hyper-leptinemia is very common in obese subjects and is a predictor of first myocardial infarction and is a risk factor for stroke (Knudson et al., 2007). Leptin is currently considered to have a part in the development of coronary artery disease in obesity (Knudson et al., 2007).

High plasma levels of Leptin have been associated with increased cytokine signaling, phagocytosis, production of pro-inflammatory cytokines like TNF- $\alpha$  and CRP, platelet aggregation and thrombosis. Leptin may also activate the sympathetic nervous system which could cause vasoconstriction, increasing vascular resistance and blood pressure (Knudson et al., 2007). Leptin may also upregulate adhesion molecules (Fantuzzi, 2008).

Although extremely high doses of exogenous leptin have been shown to cause endothelial-dependent vasodilation, this has not been shown to occur with physiologically normal concentrations. Rather, leptin concentrations similar to those observed in obese subjects may impair acetylcholine- and adenosine-mediated relaxation in cardiac vasculature (Knudson et al., 2007).

#### *Plasminogen activator inhibitor-1*

Plasminogen activator inhibitor-1 (PAI-1) is normally found in concentrations of approximately 20 ng/ml and is synthesized in, and released from, the liver and adipose tissue and is stimulated by thrombin, insulin, TNF- $\alpha$ , lipoproteins, angiotensin-2 and bacterial lipopolysaccharide (Mutch, Wilson, & Booth, 2001). PAI-1 is responsible for

decreasing the action of plasminogen activator which converts plasminogen to plasmin, a substance which breaks down fibrin in thrombi. This decrease in thrombolytic activity has been implicated in the development of atherosclerosis and endothelial dysfunction. PAI-1 levels are increased in obese subjects and visceral adipocytes release more PAI-1 than other adipocytes. Also, insulin, angiotensin 2, TNF- $\alpha$  and transforming growth factor- $\beta$  upregulate the production of PAI-1 (Mutch et al., 2001).

#### *Resistin*

Resistin is involved in insulin resistance (Knudson et al., 2007). It has been shown to impair glucose tolerance and insulin action including insulin-induced glucose uptake by adipocytes. Resistin is elevated in subjects who are obese, causes the release of endothelin-1 from endothelial cells and upregulates adhesion molecules on the endothelial cell surface. There is also some indication that it may act to reduce vasodilation by inhibiting endothelial-derived hyperpolarizing factor (Knudson et al., 2007).

#### *Tumor Necrosis Factor- $\alpha$*

TNF- $\alpha$  is an adipokine but is also secreted by endothelial cells and smooth muscle cells (Koh et al., 2005). It was one of the first to be identified as being secreted by white adipose tissue (Trayhurn & Wood, 2004). TNF- $\alpha$  is also released by macrophages within the vessel wall during the inflammatory response (Koh et al., 2005) and has been associated with insulin resistance, apoptosis, regulation of IL-6, IL-8 and haptoglobin. TNF- $\alpha$  also impairs muscle protein synthesis and may be involved in age-related sarcopenia (Lambert, Wright, Finck, & Villareal, 2008). Levels of TNF- $\alpha$  are positively

related to levels of obesity. TNF $\alpha$  is upregulated by PPAR $\gamma$  ligands (Trayhurn, 2004) and inhibited by adiponectin (Kobashi et al., 2005).

TNF- $\alpha$  is also involved in endothelial dysfunction. Elevated levels are associated with low endothelial function while lower levels are associated with improvements (Arenas et al., 2006). Administration of TNF- $\alpha$  inhibitor improved vasodilation in response to shear stress in rats (Arenas et al., 2006). It also increases expression of adhesion molecules (Edwards et al., 2007) allowing greater migration of leukocytes and increasing atherosclerosis. TNF-  $\alpha$  stimulates formation of nuclear factor-  $\kappa$ B (NF- $\kappa$ B) via stimulation of TRAF-2 which activates NIK (Celec, 2004).

### *Adiponectin*

Unlike the previously described cytokines and hormones, adiponectin is considered an anti-inflammatory molecule rather than a pro-inflammatory molecule. Adiponectin is synthesized in adipose tissue and is present in low, medium and high molecular weight forms, with the high molecular weight form the most biologically active (Sowers, 2008). It is normally present in plasma concentrations of 1.9-17.0 mg/dl, however, significantly lower levels have been reported in obese subjects and increased levels have been reported in subjects with anorexia nervosa, thus as subjects increase in body fat, paradoxically, adiponectin levels seem to decrease (Knudson et al., 2007). Adiponectin is upregulated by PPAR $\gamma$  ligands (Trayhurn, 2004) and acts through two receptors, Adipo R<sub>1</sub> and Adipo R<sub>2</sub>, which are expressed on liver and muscle tissue and in adipose cells. Increases in insulin cause a reduction in receptor expression (Sowers, 2008).

Adiponectin increases insulin sensitivity by increasing fatty acid oxidation and insulin-mediated glucose disposal and glucose uptake in skeletal muscles and decreases glucose output from the liver (H. Chen et al., 2003). Low adiponectin is associated with obesity, insulin resistance and type II diabetes (Díez & Iglesias, 2003). High molecular weight adiponectin reduces endothelial cell apoptosis, increase circulating high-density lipoproteins and reduces low-density lipoproteins, providing vascular protection (Sowers, 2008). Low plasma concentrations independently predict mortality, cardiac mortality and myocardial infarction, and are associated with increased risk of coronary artery disease, myocardial infarction, and increased platelet activation. Adiponectin may have anti-inflammatory effects as it has been associated with increased production of IL-10 and IL-1RA, reduced levels of IL-6 (Fantuzzi, 2008) and adhesion molecules E-selectin, P-selectin and ICAM-1 as well as reduced leukocyte rolling. Higher concentrations of adiponectin may reduce TNF- $\alpha$  levels and adiponectin administration has been shown to reduce blood pressure (Knudson et al., 2007). In addition, it has been shown to increase nitric oxide production in endothelial cells (H. Chen et al., 2003). Decreased levels of adiponectin may remove these protective effects. Finally, lowered adiponectin has been linked to endothelial dysfunction in obese subjects (Knudson et al., 2007).

### **Adiponectin, TNF- $\alpha$ and endothelial function**

Chronic systemic inflammation negatively affects vasodilation. Inflammation causes increases in cytokine production, synthesis of acute phase reactants, such as C-reactive protein, and the activation of inflammatory signaling pathways (Tilg & Moschen, 2006). The initiation of endothelial inflammation causes adhesion molecules on endothelial cell membranes to bind to other adhesion molecules on leukocytes and

allows the leukocytes to migrate into the vascular wall. Once there, the leukocytes attract additional leukocytes by releasing signaling molecules known as chemotactic factors and cytokines, such as IL-8. Chemotactic factors activate adhesion molecules and attract other leukocytes to affected areas of tissue. Chemokines signal leukocytes through receptors on the cell membrane and activate by way of G-proteins and are produced by both leukocytes and endothelial cells (Trowbridge, 1997).

Obese subjects have higher levels of inflammatory cytokines than lean subjects (Trayhurn & Wood, 2004). This may be caused by insufficient blood supply to the adipose tissue. The expansion of adipose tissue during the development of obesity may cause the adipocytes to become hypoxic due to a decrease in blood flow during the fat mass proliferation. An acute inflammatory response would serve to increase blood flow to that area in an attempt to relieve the hypoxia (Wang, Wood, & Trayhurn, 2007). Indeed, in areas of hypoxia, red blood cells off-load a greater amount of ATP, a stimulator for vasodilators (Mortensen et al., 2007). Ye, et al. (2007) measured oxygen tension with a needle oxygen probe in the epididymal and retroperitoneal fat pads of obese and lean mice. The  $P_{O_2}$  in the obese mice was measured at 15.2 mmHg, while the  $P_{O_2}$  in lean mice, was measured at 47.9. This would suggest that the fat pads of the obese mice were hypoxic. Additionally, adiponectin was reduced by low oxygen tension and significantly higher levels of TNF- $\alpha$  mRNA in the obese mice as compared to lean controls were observed (Ye et al., 2007). Levels of TNF- $\alpha$  are also positively related to levels of obesity and may also be increased by adipose tissue hypoxia. Wang et al. demonstrated that the relative mRNA level expressed by adipocytes of TNF- $\alpha$ , as well as



leptin, IL-6, and PAI-1, increased following chemically lowered oxygen tension mimicking hypoxia (2007).

Adiponectin inhibits the TNF- $\alpha$  stimulation of formation of NF- $\kappa$ B through several paths. TNF- $\alpha$  increases production of NF- $\kappa$ B by inducing phosphorylation of NIK into I $\kappa$ B kinase (IKK) which then induces I $\kappa$ B to undergo phosphorylation to form NF- $\kappa$ B. Adiponectin inhibits I $\kappa$ B phosphorylation through the cyclic adenosine monophosphate- protein kinase A (cAMP-PKA) pathway and by stimulating XI- $\kappa$ B which inhibits TNF- $\alpha$  stimulated NF-  $\kappa$ B (Kobashi et al., 2005) (Figure 2).

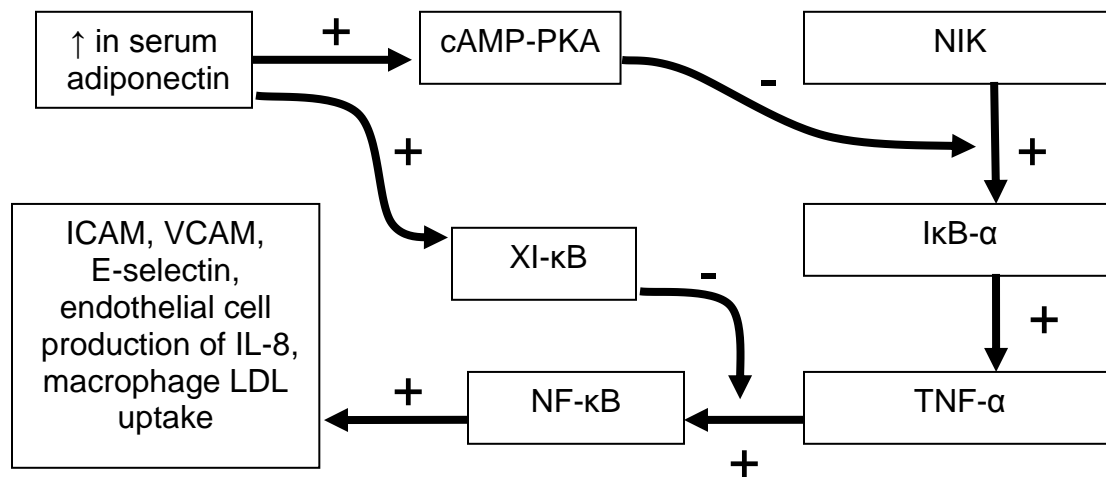


Figure 2- Adiponectin inhibits adhesion molecules, IL-8 production and macrophage LDL uptake

Also, adiponectin stimulates phosphatidylinositol 3-kinase (PI3K) phosphorylation of AKt which also inhibits NF- $\kappa$ B. (Kobashi et al., 2005). AKt also inhibits the NF- $\kappa$ B stimulation of IL-8 from foam cells (Kobashi et al., 2005). TNF- $\alpha$  stimulated NF- $\kappa$ B also induces oxidized LDL uptake by macrophages, which is inhibited when adiponectin inhibits NF- $\kappa$ B production (Matsuzawa et al., 2004; Kobashi, 2005) (Figure3). Finally, adiponectin stimulates the 5' adenosine monophosphate-activated

protein kinase (AMPK) pathway which further inhibits NF- $\kappa$ B hypoglycemia induced reactive oxygen species and prevents reactive oxygen species from oxidizing low-density lipoproteins (Devaraj, Torok, Dasu, Samols, & Jialal, 2008).

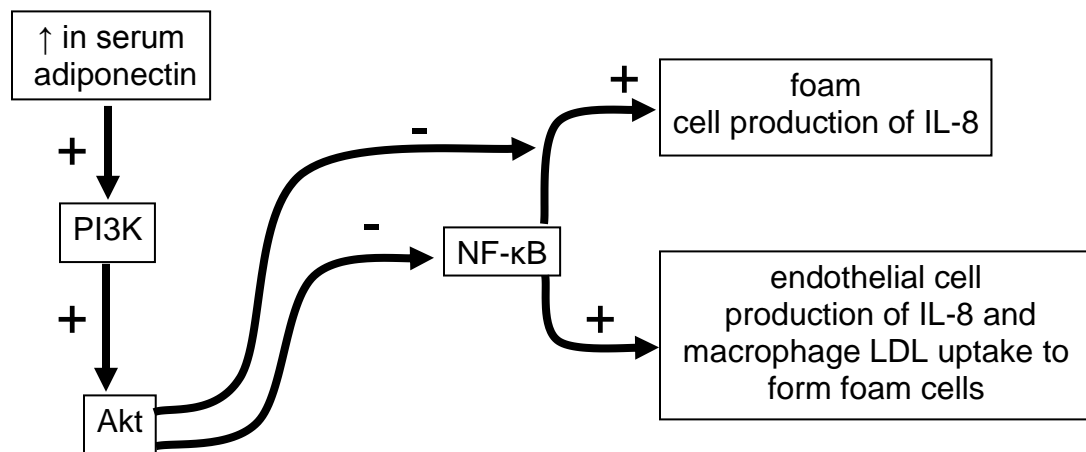


Figure 3- Adiponectin inhibits foam cell and endothelial cell production of IL-8

Additionally, TNF- $\alpha$  stimulated NF- $\kappa$ B stimulates CRP formation (Devaraj et al., 2008) and causes tissue factor to stimulate activated Factor VIIa which stimulates Factor Xa to induce thrombus formation. Adiponectin directly inhibits CRP formation and tissue factor as well as stimulating tissue factor pathway inhibitor through both the PKA and AKt pathways, possibly reducing the build up of atherosclerotic plaques (Y. Chen et al., 2008). Finally, adiponectin stimulates the release of nitric oxide by the endothelium by phosphorylation of endothelial nitric oxide synthase at Ser<sup>1179</sup> which causes vasodilation and increased blood flow (H. Chen et al., 2003).

#### *Exercise and Adiponectin*

Circulating levels of adiponectin may be influenced by exercise. Several studies of endurance exercise training found post-treatment increases in adiponectin (Eriksson et

al., 2008; Kim et al., 2007; Lim et al., 2008). Other studies have found no change in adiponectin in response to endurance exercise training (Boudou, Sobngwi, Mauvais-Jarvis, Vexiau, & Gautier, 2003; Nassis et al., 2005). Some have suggested that changes in body weight or fat mass with training may be more responsible for changes in adiponectin than the exercise training itself (Hara et al., 2005), however, studies have shown changes in adiponectin without changes in body weight (Fatouros et al., 2005; Hojbjerg, Rosenzweig, Dela, Bruun, & Stallknecht, 2007) so the mechanism remains unclear.

The effects of an acute bout of endurance exercise on levels of plasma adiponectin are also unclear. Again, studies have shown no changes in plasma adiponectin levels following a bout of exercise (Ferguson et al., 2004; Jamurtas et al., 2006; Punyadeera et al., 2005), while other studies have demonstrated increases (Jurimae et al., 2006; Kraemer et al., 2003) and others have shown decreases in adiponectin (Jurimae et al., 2005; Yatagai et al., 2003). Studies which showed increases in adiponectin utilized high intensity exercise, such as 90-100%  $\text{VO}_{2\text{max}}$  (Kraemer et al., 2003) or a 2000 meter rowing time trial, while those without significant results tended to use a lower intensity. Interestingly, the studies which showed a decrease also used higher intensity exercise bouts. Jurimae suggested that this may indicate insufficient recovery (Jurimae, Purge, & Jurimae, 2006) or it may indicate that the bout may have exhausted or overtrained the subjects.

Two studies which examined the effect of an acute resistance exercise bout demonstrated mixed to positive results. Jurimae et al. (Jurimae et al., 2005; Jurimae et al., 2006) found changes in adiponectin in response to an acute bout of rowing, however,

adiponectin only increased in the group of elite rowers that were selected for the national team. In the other two groups, adiponectin levels were reduced following exercise. The results, however, are difficult to generalize as all subjects were described as “elite” level rowing athletes. Rowing has been noted to be a unique form of exercise as it involves a somewhat resistance exercise-like component when starting from a dead stop, then becoming aerobic exercise as the speed is maintained for the remainder of the bout (Cook et al., 2006). More recently, Varady, et al. (2009) had 4 groups complete a bout of acute resistance exercise using a leg press for 8-12 repetitions. The four groups were all male, lean with a mean age of 26. One group was sedentary, one was resistance trained, one endurance trained and one was both resistance and endurance trained. The two groups who were resistance trained demonstrated significant increases in adiponectin of 30-37% while the other two groups showed insignificant increases. Flow-mediated dilation increased in all three trained groups, but not the sedentary group (Varady et al., 2009).

Fatourous et al. (2005) utilized resistance exercise as a stand-alone intervention, however, this was a treatment study, rather than an acute bout of exercise. This study utilized three groups, each performing resistance exercise training at different intensities; a light group utilizing 45-50% of one repetition maximum (1RM), a moderate group utilizing 60-65% 1RM, and a high intensity group utilizing 80-85% 1 RM. The light group did not experience an increase in plasma adiponectin (though there was a trend), but the moderate group and high group both increased plasma adiponectin, with the high intensity resistance training generating the largest increase in plasma adiponectin. This may indicate that responses of adiponectin to resistance exercise, like aerobic exercise, may be intensity dependent.

An examination of studies to determine the time course of changes in adiponectin following a bout of endurance exercise shows that few measured adiponectin after more than one-half hour after exercise (Hojbjerre et al., 2007; Jamurtas et al., 2006; Kraemer et al., 2003; Punyadeera et al., 2005) though Jamurtas (2006) measured adiponectin more than two and a half hours post exercise (Figure 4).

Jamurtas (2006) did not show any changes in response to endurance exercise at immediately post or at 24 or 48 hours. Figure 4 displays only the results up to two and a half hours post exercise.

Jurimae et al. (2005; 2006) and a high intensity group in a study by Kraemer et al. (2003) demonstrated greater adiponectin levels thirty minutes post exercise compared with directly post exercise, though Jurimae did not measure after 30 minutes. The low intensity group in the study by Kraemer et al. (2003) measured adiponectin immediately post and found higher post-exercise levels compared with thirty minutes post. Punyadeera et al. found similar results (2005). Ferguson et al. (2004) and Varaday et al. (2009) only measured post-exercise and also found elevated adiponectin. One study found no improvements in adiponectin (Diabetes Research in Children Network (DirecNet) Study Group, 2008). These data suggest that peak post-exercise adiponectin values occur directly post-exercise or at 30 minutes post exercise. However, two studies which measured at one hour also measured at 30 minutes and found very similar values of adiponectin. Very few data exist regarding adiponectin levels more than two and a half hours post exercise.

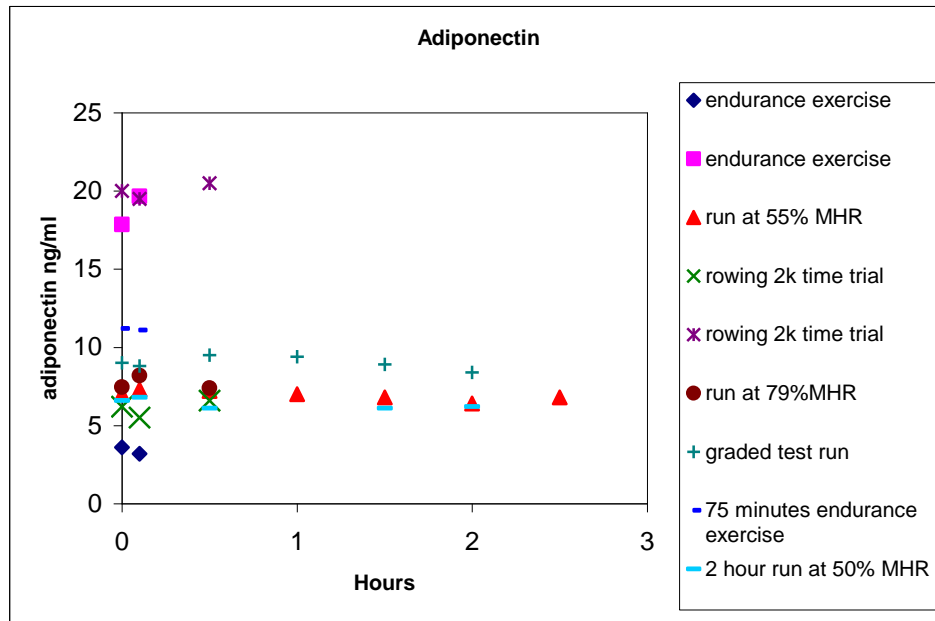


Figure 4- Time course of changes in adiponectin following acute exercise

Since, resistance exercise increases blood flow and blood pressure when performing exercises utilizing a high intensity and a large muscle mass (Focht & Koltyn, 1999), this action may result in “washout” of adiponectin from interstitial spaces and into the blood stream or may up-regulate an active transport system (Hojbjerre et al., 2007) causing increases in plasma adiponectin. It appears as though higher intensity exercise may be necessary to generate this effect. Alternately, an increase in blood flow may reduce the hypoxic environment in the adipose tissue and reduce inflammation following an acute bout of resistance exercise (Focht & Koltyn, 1999).

#### *TNF- $\alpha$ and Exercise*

Research suggests that TNF- $\alpha$  may be reduced following a bout of resistance exercise. Tsai et al. had subjects who were hockey players perform a 60 minute bout of resistance training at 50% of 1RM for three sets of eight repetitions with six exercises. Twenty four hours following the bout, TNF- $\alpha$  was significantly reduced from baseline,

though it was no longer significantly reduced at 48 hours post (Tsai et al., 2006).

Conversely, other researchers have found an increase in TNF- $\alpha$  mRNA following a 120 minute bout of resistance exercise utilizing four sets of 10 repetitions with 60% of 1RM with ten exercises with strength trained subjects (Nieman et al., 2004). There is a large difference, however, in the volume of exercise in these two studies, so comparisons are difficult to interpret. Resistance exercise may cause an overall reduction in TNF- $\alpha$  due to an increase in adiponectin. However no study has examined the effects of adiponectin on TNF- $\alpha$  following a bout of resistance exercise.

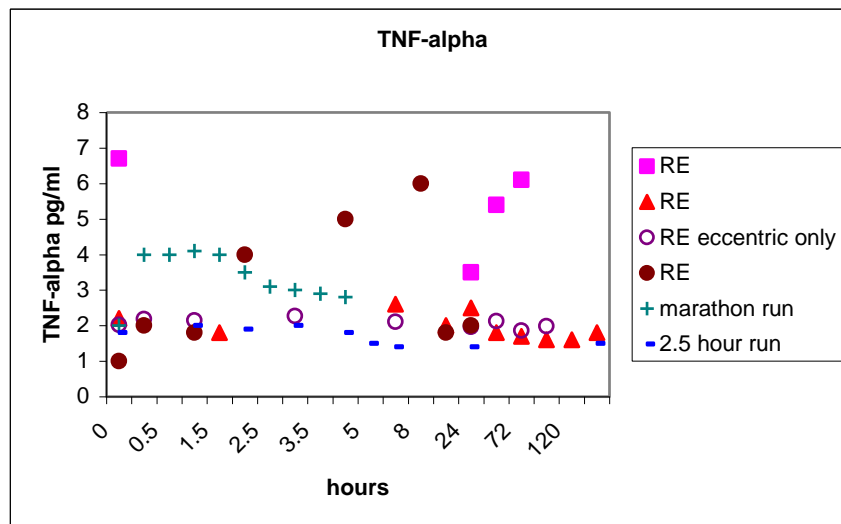


Figure 5- Time course of changes in TNF- $\alpha$  following acute exercise

The time course of changes in TNF- $\alpha$  suggests that it may demonstrate the largest change within 24 hours post exercise. Figure 5 summarizes the pertinent studies.

Three studies measured TNF- $\alpha$  immediately post exercise (Hirose et al., 2004; Louis, Raue, Yang, Jemiolo, & Trappe, 2007; Ostrowski, Rohde, Asp, Schjerling, & Pedersen, 1999) and all demonstrated an elevation in TNF- $\alpha$  at that time point. At one hour, all three found levels approximately equal to immediately post while a fourth (Ostrowski et al., 1998) found levels slightly higher than pre-exercise. At two hours, one

study showed further increases (Louis et al., 2007) (and increased up to 8 hours post-) while the two others began to decline (Hirose et al., 2004; Louis et al., 2007; Ostrowski et al., 1999).

At 24 hours post exercise, three studies observed TNF- $\alpha$  at levels below pre-exercise (Hirose et al., 2004; Ostrowski et al., 1998; Y. M. Tsai et al., 2006) while two other studies demonstrated higher levels (Louis et al., 2007; Smith et al., 2000) with the one by Smith et al. peaking at 24 hours while levels in the previous study were the lowest at 24 hours, but climbed at 48 and 72 hours. Overall, three of the five studies that measured TNF- $\alpha$  at baseline and at 24 hours post-exercise observed the largest change from baseline at that time point (Hirose et al., 2004; Ostrowski et al., 1999; Y. M. Tsai et al., 2006). The largest changes in TNF- $\alpha$  seem to be observed immediately post exercise, one hour post-exercise and/or 24 hours post-exercise.

### **Exercise effects on endothelial function**

Exercise has been shown to alter endothelial function. Numerous studies have shown increases in vasodilation after acute endurance exercise and endurance exercise training. Resistance training, however has shown to have smaller effects on vascular function including some studies that indicate there may be decreases in some measures post-training. Acute resistance exercise has not been well studied, however, with only five studies to date examining the post-exercise effects, none utilizing forearm blood flow.

#### *Endurance Training*

Hambrecht, et al. (1998) enrolled ten heart failure patients into an exercise program consisting of six bouts of ten minutes on a bicycle ergometer at 70% of heart



rate at peak oxygen uptake for three weeks in a supervised hospital environment. For five additional months, they were asked to exercise at home on a loaner ergometer for 40 total minutes a day, five days a week and attend one group training session each week. A control group did not participate in exercise. After six months, the subjects' peak oxygen consumption increased by 26%. Additionally, peripheral blood flow, measured at the femoral artery, was significantly improved in response to a dose of acetylcholine (+187%). The increase in flow was due mainly to an increase in blood flow velocity, suggesting that the exercise program improves peripheral blood flow by improving endothelium-dependent vasodilation in resistance vessels. Following training, the inhibition caused by a dose of L-NMMA significantly increased by 174% indicating an improvement in the function of nitric oxide. No significant changes occurred in the control group (Hambrecht et al., 1998).

The same effects hold true when the endurance training involves young healthy males. Clarkson et al. (1999) recruited 25 healthy military recruits aged 17-24 years and followed them during their ten week basic training, measuring arterial diameter via ultrasound both at rest and in response to reactive hyperemia. After training, the flow-mediated dilation significantly increased from a mean of 2.2 to 3.9% while there was no change in response to glycerol trinitrate.

This study suggests that even healthy, young individuals can realize improvements in vascular functioning through endurance exercise. The improvements were generated even when the exercise group experienced an overall rise in total cholesterol and a decrease in high-density lipoproteins and no changes in levels of lipoprotein (a), or fibrinogen (Clarkson et al., 1999). The authors suggest that regular

exercise causes frequent increases in endothelial shear stress which may lead to increases in nitric oxide production mediated by an increase in nitric oxide synthase.

A cross sectional study by Kingwell et al. (1996), used athletes as subjects and demonstrated a significant difference between endurance trained subjects and controls with the athletes experiencing a reduction in vascular resistance of 71% compared to 55% in the controls ( $p = .03$ ) in response to a dose of acetylcholine.

There are some indications that endurance exercise may cause endothelial progenitor cells to be released by the bone marrow. Steiner et al. (2005) examined the effects of a 12 week endurance exercise training program involving 30-60 minutes of aerobic exercise three times a week on angiogenic growth factors and flow mediated dilation of the brachial artery. The exercise group experienced a  $2.9 \pm 0.4$  fold increase in the number of endothelial progenitor cells as compared to controls and a  $1.05 \pm 0.02$  fold increase in flow mediated dilation which was positively correlated ( $r = 0.81$ ) with the increase in endothelial progenitor cells. The authors hypothesized that the formation of atherosclerosis may be partially due to an exhaustion of the endothelial progenitor pool. This study indicates that endurance exercise can increase the pool supply of progenitor cells. Statins have also been shown to increase the pool supply as well.

#### *Acute Endurance Exercise*

Endothelial function increases following a single bout of endurance exercise. Haram et al. (2006) examined abdominal aorta functioning in both untrained and endurance trained rats following a one hour endurance exercise bout at 80-90% of maximal oxygen uptake. The untrained rats demonstrated a decrease in vasodilation in response to increasing doses of acetylcholine at zero and six hours, then an increase from

12 to 48 hours, after which vascular responsiveness returned to baseline. The trained rats did not demonstrate the same biphasic response, but showed no change immediately post exercise, then an increase in vasodilation from 6 hours to 96 hours. The trained group returned to baseline by the eighth day measurement. Acute endurance exercise in humans also led to vasorelaxation in another study examining young African-American and White men. Central pulse wave velocity was unchanged while peripheral pulse wave velocity was decreased in the white males, though not in the African-American males (Heffernan, Jae, & Fernhall, 2007).

In examining the magnitude of change of forearm blood flow following endurance exercise with intensities ranging from 50% to 100% of maximal oxygen consumption, pretest forearm blood flow ranged from a mean of 3.3 to 23.5 ml·100ml<sup>-1</sup>·min<sup>-1</sup> (Baynard, Miller, & Fernhall, 2003; Baynard, Jacobs, Kessler, Kanaley, & Fernhall, 2007; Bousquet-Santos, Soares, & Nobrega, 2005; Goto et al., 2003; Goto et al., 2007; Umpierre, Stein, Vieira, & Ribeiro, 2009;. Several studies (Baynard et al., 2003; Baynard et al., 2007; Bousquet-Santos et al., 2005; Goto et al., 2003; Goto et al., 2007; Umpierre et al., 2009) have demonstrated a mean increase immediately following the bout of exercise. Only two studies, however demonstrated elevations above pre-exercise values at one hour (Bousquet-Santos et al., 2005; Umpierre et al., 2009), but both values were lower than values immediately post-exercise. Thus, it appears as though forearm blood flow peaks immediately post-exercise. Few studies have measured time points beyond post-exercise and the results were not different those at 1 hour post-exercise.

Other measures of endothelial function (pulse wave velocity and flow-mediated dilation) found no difference in the dependent variable more than one hour post-exercise.

The two studies which utilized PWV (Heffernan, Collier, Kelly, Jae, & Fernhall, 2007; Heffernan, Jae, Echols, Lepine, & Fernhall, 2007) found improvements 30 minutes post-exercise above those pre-exercise, but the improvements were smaller than those immediately post-exercise (improved PWV results in lower values while improved FMD results in higher values). Another study examined FMD after endurance exercise, but only measured one hour after exercise and FMD was still elevated in all groups except the sedentary, which was lower (Harris, Padilla, Hanlon, Rink, & Wallace, 2008).

The response to exercise may also vary according to where the conduit vessel is located. Wray et al. (2005) compared the arterial dilation response of the brachial artery during hand grip exercise with the deep femoral artery and common femoral artery during knee-extensor exercise and found that the deep femoral artery dilated in response to shear stress to a greater degree as compared to the common femoral artery or the brachial artery, both of which responded similarly. The authors hypothesized that the deep femoral artery is closer to the exercising muscle and may have been more affected by local metabolite release, though any of the three sites could have been affected by local release of metabolites, which confounds pinpointing the mechanism of the vasodilation.

In contrast, inactivity may contribute to endothelial dysfunction in humans. One study compared flow-mediated dilation in response to an acute bout of endurance exercise in overweight males. One group was active, as defined by the Surgeon General's guidelines, while the other was inactive. The inactive group experienced a decrease in flow mediated dilation following a one hour bout of endurance exercise while the active group demonstrated an increase (Harris et al., 2008). Typically, overweight

individuals have a decreased endothelium-dependent vasodilation compared to normal weight subjects (Higashi, Sasaki, Nakagawa, Matsuura, Chayama et al., 2001) .

Overall, it appears as though post-exercise endothelial function improvements, in particular forearm blood flow, are greatest directly following the exercise bout and continue to be elevated, but at a diminished level, for at least one hour following exercise.

### *Resistance Training*

Endurance training is more frequently studied than resistance training, however, resistance exercise may also be of some benefit to vascular function as well as providing increased capacity in activities of daily living, a greater ability to exercise aerobically, a maintenance of strength during aging, a greater caloric expenditure in spontaneous physical activities and lowered blood pressure (Umpierre et al., 2009). Baynard, Miller and Fernhall (2003) compared the forearm blood flow via strain-gauge plethysmography in two groups before and following a maximal aerobic exercise bout. One group had participated in endurance training and the other in resistance training for at least one year prior to the study. Resting blood flow was higher in the resistance training group though the endurance group exhibited a higher response to reactive hyperemia prior to the exercise bout. Following the maximal aerobic exercise bout, there was no difference in forearm blood flow between the two groups (Baynard, 2003). The differences in resting blood flow may have been present because of a greater forearm muscle mass in the resistance trained group. Varady, et al. (2009) examined FMD following a single bout of leg press exercise in four groups, a sedentary group, a resistance trained group, an endurance trained group and a group which was both resistance trained and endurance trained. All three trained groups demonstrated improved FMD following resistance

exercise, but the untrained group showed impaired vasodilation. These studies suggest that both resistance training and endurance training are equally beneficial to endothelial function.

Olson et al, (2006) examined the effect of beginning a resistance training program, randomizing 30 overweight women into a training and control group. The training group participated in resistance training for one year, twice a week. The resistance training group significantly improved strength and lean body mass, but did not reduce weight nor body mass index. The resistance trained group significantly improved flow mediated dilation assessed via ultra sound at the brachial artery versus the control group. This would indicate that a resistance training program alone would improve vascular function (Olson et al., 2006).

A notable concern, however, is the possibility that resistance exercise may cause a decrease in central arterial compliance. Miyachi et al. (2003) examined young and middle aged males who participated in resistance training but not endurance training and compared them to sedentary males of the same age. The researchers found that the middle aged resistance trained males had 30% lower carotid artery compliance than their sedentary counterparts. The authors speculated that this could be because the high pressures generated during resistance training caused hypertrophy of the arterial smooth muscle cells, as the resistance trained males had a significantly thicker carotid intima thickness. The decrease in compliance correlated significantly to years of resistance training experience. They speculated that this adaptation may be a protective mechanism against a possible arterial rupture due to the high pressures during resistance training (up to 320/250 mmHg) or a mal-adaption or both. Interestingly, the peripheral arteries,

brachial and femoral, did not show a decrease in compliance, probably due, the authors suggest, to the lower pressures at those locations. Additionally, the blood pressures measured in all groups were normal and not significantly different. More research to determine if this adaptation is harmful is warranted.

Kawano, Tanaka and Hiyachi (2006) placed men into three groups; resistance training only, combined resistance and endurance training and a sedentary control for four months of three day a week training followed by four additional months of detraining. At the end of the training period, the strength training only group experienced a significant reduction in carotid artery compliance while the combination group did not experience a significant change. Again, peripheral artery compliance did not change. The intima thickness of the carotid artery did not change for any group, however, and the resistance training group had a significant decrease in brachial diastolic blood pressure, from 71 to 66 mmHg while the combination group experienced no decrease and neither group had a significant change in carotid blood pressure. Both resistance training groups experienced an increase in left ventricular wall thickness and mass as well. After deconditioning, all values returned to pre-training values. A limitation of this study, though was a different resistance training protocol for the two groups. The combination group used a three set, 8-12 exercise plan at 80% of 1 RM while the resistance training only group used a three set, 14-16 exercise plan at 50% of 1 RM. Consequently, the combination group produced much larger increases in strength (25% vs. 10% in the squat, for example). One could argue that the changes in compliance could be explained by the differences in the strength training programs. The authors chose the low intensity program for the resistance training only group to emphasize that even a light resistance

training program could cause the negative changes in compliance (Kawano, Tanaka & Miyachi, 2006).

#### *Acute Resistance Exercise.*

The effects of acute bouts of resistance exercise are not well studied. Only five studies have examined the acute effects of resistance exercise. Three of the five had the same lead author (Heffernan et al., 2007; Heffernan, Jae et al., 2007; Heffernan, Jae, Edwards, Kelly, & Fernhall, 2007; Heffernan, 2006; Heffernan, 2007) and all examined healthy young adults. Heffernan (Heffernan, Jae et al., 2007) and Varaday et al. (2009) observed overall positive effects and one mixed to positive effect (Heffernan et al., 2006). Two negative effects were also observed (DeVan et al., 2005; Heffernan, Jae, Edwards et al., 2007). The three studies by Heffernan et al. all used pulse wave velocity and no study utilized strain-gauge plethysmography. In two of the studies (DeVan et al., 2005; Heffernan, Jae et al., 2007), the bout of exercise involved the forearm musculature which may cause changes in blood flow due to local metabolite release rather than shear stress or systemic effects. The other three studies (Heffernan et al., 2006; Heffernan, Jae et al., 2007; Varady et al., 2009) utilized resistance exercise only with the lower body then measured either flow mediated dilation, central pulse wave velocity or leg pulse wave velocity. There was no change in the central measures, brachial or carotid pulse wave velocity or in the non-exercised leg but there were decreases in pulse wave velocity in the exercised leg. Varaday et al. (2009) examined flow mediated dilation after a maximal bout of leg press in three trained groups and one untrained group, all of normal weight and BMI. The trained groups demonstrated increases in vascular function following the bout of leg press, but the untrained group did not. Because all subjects were lean, it is



unknown if the effects would have been different between lean and overweight subjects. (Varady et al., 2009) Additionally, no study has examined forearm blood flow in response to a hyperemic stress with plethysmography following a bout of lower body resistance training. This would minimize the response of the forearm vasculature to local metabolite release.

Utilizing leg flexors and extensors during a resistance exercise bout would include a large muscle mass, but not involve the muscle in the region measured. If changes occur in forearm blood flow in response to leg exercise, it could be hypothesized that those changes were occurring systemically. Baynard, Miller and Fernhall (2003) examined forearm blood flow in both endurance and resistance trained individuals following a maximal bout of treadmill exercise and found improved forearm blood flow following the exercise bout in both groups. This may indicate a systemic effect on endothelial function following lower body endurance exercise.

## **Summary**

Endothelial function is the ability of arteries to dilate in response to increases in shear stress due to increases in blood flow and is mediated primarily through nitric oxide and other vasodilators released by endothelial cells. These cells form a single layer intima which lines the lumen of the artery, separating the contents of the artery lumen from the smooth muscle layer which surrounds it and controls artery diameter. Systemic inflammation negatively affects endothelial function and is present in obesity causing arterial stiffening and eventually leading to atherosclerosis. A number of cytokines, which work as chemical messengers in the vascular system, regulate this systemic inflammation. Adiponectin and tumor necrosis factor- $\alpha$  are two of the primary cytokines

that influence vascular functioning directly and through effects on inflammation with adiponectin having anti-inflammatory effects while the effects of tumor necrosis factor- $\alpha$  are pro-inflammatory. Obesity is strongly correlated with both higher levels of TNF-  $\alpha$ , lower levels of adiponectin as well as endothelial dysfunction.

Endurance exercise has been shown to increase endothelial function, both as a consequence of training and within the first hour following a single bout. Resistance exercise, however, has not been as well studied. Resistance training studies have shown mixed results, with most studies showing an increase in vasodilation but some showing losses in endothelial function. Acute resistance exercise has been used in very few studies, again with inconsistent results. None of these studies, however, have used obese subjects, so the effects of acute resistance exercise on the endothelial function of obese versus lean individuals is unknown. Additionally, no study has examined the effects of acute resistance exercise for more than one hour post exercise and none have examined the effects of the bout on adiponectin and TNF-  $\alpha$  in obese subjects.

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## **The effects of resistance training on brachial flow-mediated dilation: a meta-analysis**

### **Abstract**

Resistance Training Effects on Brachial Artery Flow Mediated Dilation: A meta-Analysis. **Introduction:** A meta-analysis of the effects of resistance training (RT) on brachial artery flow mediated dilation (FMD) was performed. **Methods:** A search of online data-bases was conducted in the first quarter of 2008. Studies which examined FMD and utilized whole body RT were included. Studies were excluded if the RT protocol used less than half of all major muscle groups or if insufficient information was available to generate effect sizes (ES). Articles which assessed two RT treatment groups were divided into separate ES. Ninety-six studies were evaluated. Studies were also coded for training variables. **Results:** Twelve studies formed 14 pre- to post-treatment ES and 9 treatment versus control ES. RT created an overall positive pre-test to post-test mean ES (standard difference in the mean = 0.458, SE = 0.144, 95% CI (0.176, 0.741),  $z = 3.177$ ,  $p = 0.001$ ). Meta-regression was used to determine correlations between RT moderator variables. Although several training variables did significantly correlate to FMD (age, percent of 1 repetition max, number of repetitions per set, number of sets per exercise, and length of interest rest:  $p < 0.05$ ), point estimates were small indicating little effect. **Conclusions:** These results indicate that RT appears to have a small positive effect on FMD. **Key Words:** WEIGHT TRAINING, ENDOTHELIAL DYSFUNCTION

## Introduction

Brachial flow-mediated dilation (FMD) is the most commonly employed technique for the evaluation of endothelial or vascular function. Vascular function has been shown to be a good predictive indicator of cardiovascular events. In a study evaluating patients with peripheral vascular disease, Gokce, et al. (2003) observed that 25% of subjects with the lowest two thirds of brachial artery FMD values ( $<8.1\%$  increase from baseline) suffered from a cardiovascular event within three years compared to 3% in the highest one third of FMD values ( $>8.1\%$ ) (2003). In the Framingham Heart Study, endothelial function was examined via FMD in 2883 individuals (mean age 61years). Significant negative correlations were found between both absolute and percent change in FMD, Framingham risk score, and a combination of covariates including age, systolic blood pressure, diastolic blood pressure, diabetes, smoking, LDL/total cholesterol, and HDL cholesterol (Wilson et al., 1998).

Both acute and chronic endurance exercise training have been shown to be effective in improving endothelial function (Hambrecht et al., 1998; Kingwell, Tran, Cameron, Jennings, & Dart, 1996); however, studies evaluating the effects of acute and chronic resistance training on endothelial function have been equivocal. Several training studies (Anton et al., 2006; Cook et al., 2006; Copeland et al., 1996) have demonstrated improvements in vascular function following resistance exercise training while others (Cortez-Cooper et al., 2005; Miyachi et al., 2003; Miyachi et al., 2004) have reported reductions in endothelial function following training. It has been suggested that this may be due to adaptive structural changes in smooth muscle, collagen, or elastin in the arteries in response to the elevated blood pressures produced during resistance exercise (Bertovic

et al., 1999). Additionally, it has been suggested that the vascular adaptations to resistance training may vary between conduit and resistance arteries (Heffernan et al., 2006)

Despite these equivocal results, there seems to have been generated in the literature the general belief that resistance training decreases endothelial functioning. This is perhaps because no study has directly examined the overall results of the multiple studies that have been conducted using resistance training as a treatment and endothelial function as an outcome. A meta-analysis allows for an objective assessment of the effects of a treatment or treatments by following established statistical guidelines (Peterson, Rhea, & Alvar, 2005) where each study is used to generate an effect size, a data point, which are then combined to produce an overall evaluation of those effects. A recent comprehensive literature search failed to reveal a published article evaluating the effects of resistance training on vascular function through meta-analytic techniques.

The purpose of this study was to determine the effect of resistance training on brachial artery flow mediated dilation utilizing meta-analytic techniques. Additionally, we sought to assess whether differences in moderating variables, including exercise intensity, number of repetitions per set, number of sets per exercise, number of exercises per session, number of sessions per week, number of weeks of training, length of inter-set rests, inclusion of concurrent aerobic activity and completing repetitions to failure, have any specific effects on vascular function.

## **Methods**

The experimental hypothesis for this meta-analysis was that resistance training has an overall positive effect on brachial artery flow-mediated dilation following an ischemic



stress and that improvement differs with the training variables involved, such as intensity, number of repetitions, sets or training frequency.

*Procedures.* A literature search was performed in the first quarter of 2008 of the online data-bases Pubmed, Sport Discus and Dissertation Abstracts Online. Studies must have examined vascular function utilizing brachial artery flow-mediated dilation and utilized whole body resistance training. Non-English language articles, studies which used resistance training for less than half of all major muscle groups, or studies which did not provide enough information to generate effect sizes were excluded. The search terms “resistance training,” “strength training,” “weight lifting,” “weight training,” “endothelial function,” and “vascular function” were used. Articles were first found by title then by examining the abstract. Once an article was chosen for full review, the bibliography was hand searched in the same manner. When data needed to create effect sizes were missing, at least two attempts were made to contact authors via e-mail to obtain the necessary data.

Articles which contained two resistance training treatment groups were divided into two effect size groups and separate articles which provided information about the same treatment group were combined into a single effect size group. A total of 98 studies were reviewed and sorted with a total of 12 chosen for inclusion in this study. The 12 studies formed 14 study groups that were included in the analysis. Figure 1 illustrates the classification of reviewed papers.

*Statistical analysis.* Articles were coded for mean percent of one repetition max as a measure of exercise intensity, mean number of repetitions per set, mean number of sets per exercise, mean number of exercises per session, mean number of days per week,

mean length of rest interval between sets, number of weeks of training, whether an aerobic warm up was performed, whether aerobic exercise other than a warm up was performed, whether exercises were done to volitional failure, and the average age of the subjects and effect sizes were generated for pretest to post test measures as well as post test to control when available. Pre-test versus post-test effect sizes were generated with the following equation:  $ES = (X_{\text{post}} - X_{\text{pre}}) / SD_{\text{pre}}$  where  $X_{\text{post}}$  is the measurement following treatment,  $X_{\text{pre}}$  is the measurement before treatment and  $SD_{\text{pre}}$  is the standard deviation of the pre-treatment measure (Coe, 2002).

In the case of Post-test versus control, effect sizes were generated with the following equation:  $ES = (X_{\text{post}} - X_{\text{con}}) / SD_{\text{pool}}$  where  $X_{\text{post}}$  is the measure following the treatment,  $X_{\text{con}}$  is the measure of the control subjects and  $SD_{\text{pool}}$  is the pooled standard deviation of both groups using the equation in Figure 2 where  $N_e$  is the number in the experimental group,  $SD_e$  is the standard deviation of the experimental group,  $N_c$  is the number in the control group and  $SD_c$  is the standard deviation of the control group (Coe, 2002). All statistical analysis was performed using commercially available software (Comprehensive Meta-Analysis, Biostat, Englewood, NJ).

## Results

Table 1 summarizes the study groups included in the analysis. Although the mean age of the study groups' subjects was 31.8 years, only one study used subjects with a mean age between 21 and 38 years (Rakobowchuk et al., 2005). Additionally, 13 of the 14 study groups included an aerobic exercise warm up and ten of the groups included an aerobic exercise component in the training program. Only Rakobowchuck (2005) did not

include any aerobic exercise. Four of the study groups reported performing repetitions to failure, six reported not completing repetitions to failure, and four did not report.

A summary of the training variables reported in each study are included in Table 2. Overall, there was a significant positive standard difference in the means of 0.458 (SE = 0.144, 95% CI (0.176, 0.741),  $z = 3.177$ ,  $p = 0.001$ ) indicating an increase in percent brachial flow-mediated dilation after treatment. A summary of the standard difference in the means of each study group with the associated forest plot is included in Figure 3. The residuals of the studies with both the largest and smallest standard difference in the means were large, but the result remained significant when one or both were removed from the analysis.

Each training variable was then analyzed utilizing meta-regression. A summary of the study groups' training variables which produced a significant result is included in Table 3. Although some moderating variables did produce a significant result, the slope for each was small, indicating much variance was unaccounted for in each analysis. Thus, FMD seems unaffected by subject age, warm-up, cardiovascular training, weeks of training, days per week of training, number of exercises, number of sets, number of repetitions per set, intensity, repetitions to failure, or length of inter-set rests.

## **Discussion**

Our meta-analysis observed a moderately positive (0.458) overall standard difference in the means, which would indicate that brachial FMD improves following resistance training. Miyachi et al. (2004), observed decreases in conduit vessel compliance following RT and hypothesized that RT would cause decreases in the artery's ability to dilate under shear stress due to vessel stiffening in response to increases in

blood pressure generated during RT. Indeed, blood pressures as high as 350/280mmHg have been recorded during maximal resistance exercise involving leg presses at 90% 1RM to failure (MacDougall, Tuxen, Sale, Moroz, & Sutton, 1985). However, the long term effects of RT on systemic blood pressure are usually positive. A meta-analysis by Cornelissen and Fagard (2005) examining blood pressure and resistance training in 12 randomized controlled trials found a decrease in resting diastolic BP of -3.5mmHg ( $P<.01$ ) and a decrease in resting systolic BP of -3.2 mmHg ( $P=0.10$ ) (2005). The authors suggest that decreases in BP may be due to decreases in sympathetic tone, though decreases do not always occur with training they noted. Also, in the studies reviewed in the meta-analysis that tested maximal oxygen consumption,  $\text{VO}_2$  max increased by 10.5%, comparable with aerobic-based interventions of the same length (2005).

In our analysis, all but one group (Rakobowchuk et al., 2005) used cardiovascular training concurrently with RT. Rakobowchuck allowed subjects to continue a limited amount of cardiovascular training if they were already engaged in that training prior to the study. This creates difficulty in determining the effect of the RT versus the cardiovascular exercise, as even only a short warm up may have an effect on FMD. The inclusion of RT, however, did not prevent an improvement in FMD, suggesting that it may be safe to include in a training program with risk of diminishing flow mediated dilation.

Only two groups experienced a decrease in brachial FMD (Casey, Pierce, Howe, Mering, & Braith, 2007; Okamoto, Masuhara, & Ikuta, 2007; D. P. Casey et al., 2007). Casey also reported increases in carotid to radial and carotid to femoral pulse wave velocity, another measure of conduit artery functioning which measures the speed at

which a pulse wave moves through the circulatory system. Stiffer arteries produce faster moving waves. Huang et al. (2007), found that among patients with peripheral artery disease, FMD of 4.2-7.9% would place patients in the middle tertile which had higher rates of coronary events than the highest tertile with FMD >8%. However, the RT treatment moved the mean subject in these studies from the lower end of the tertile range to the higher end. Additionally, the one group in this analysis which did not include any aerobic training would have scored in the highest tertile. Lastly, patients in the study by Huang who experienced cardiovascular events had a mean FMD of  $4.5 \pm 3.0$  while those who did not had FMD values of  $6.9 \pm 4.6\%$ , lower than the mean FMD of these studies.

While the notion that RT reduces FMD has gained popularity in the scientific literature, a thorough, systematic examination of published research studies to date suggests that RT, at worst, has little to no effect on FMD, and may improve functioning for some individuals. One difficulty of evaluating any exercise treatment is accounting for the physical activity that occurs outside the research environment. Although subjects are instructed to maintain normal activity levels and not increase exercise, some research indicates that as individuals become stronger through RT, they may increase spontaneous physical activity (Hunter, 2005). This extra physical activity may affect endothelial function.

Few of the studies evaluated RT in isolation. Most included some form of aerobic training, even if only as a warm up. Because the long-term effects of very short bouts of aerobic exercise on a regular basis is unknown, even aerobic warm ups may have an effect on endothelial function beyond that of RT alone.

There are several limitations of the current study including the use of only simple correlations. Interactions may exist which affect the validity of the correlations. Less than two-thirds of the study groups utilized a control group leading to lower statistical power. Some studies used only pre-tests with the control group rather than both a pre- and post- design, reducing reliability. Also, in this analysis, two study groups are actually a single group at two different time points, 6 weeks and 52 weeks (Woo et al., 2004).

With regard to the RT moderating variables, higher intensities of RT, expressed as a percentage of 1 RM, lower numbers of repetitions per set, and longer inter-set rests are usually prescribed together and the effects of one of the variables is confounded by the changes in the others. Additionally, many RT variables were not reported, especially inter-set rests, load expressed at a percent of 1RM, or whether the subject lifted to momentary muscular failure. These important variables for designing strength programs may have an important effect on endothelial function as well and should be reported. Another limitation was that many studies presented only figures without the data point numbers, though efforts were made to obtain all necessary data for analysis. Upon contacting the corresponding authors, most were very generous with providing the necessary information, but some data were still unobtainable.

Finally, the collection of studies used very heterogeneous groups of subjects. Although 9 used healthy young adults under the age of 50, others used older adults, adults with type two diabetes and heart failure, overweight subjects or subjects with high levels of cholesterol or a combination of chronic diseases. The variability of the subject populations may have obscured possible trends in the data..

*Future research directions.* This study only examined studies of endothelial function as measured by percent change in FMD with a resistance training treatment. Acute and cross sectional studies should also be analyzed to determine those effects as well. Additionally, more training studies utilizing only RT versus RT with aerobic warm up versus RT with aerobic training should be performed to determine the actual RT-only effects on endothelial function. Studies which use RT as a treatment should evaluate endothelial function utilizing other techniques including forearm blood flow, pulse wave velocity and intima-media thickness. Additionally, multiple methods of endothelial function assessment should be used in each study to determine whether changes are systemic or restricted to only conduit arteries or resistance arteries. Finally, the mechanisms underlying such changes should be examined including myogenic causes as well as changes in cytokines, metabolites and hormones.

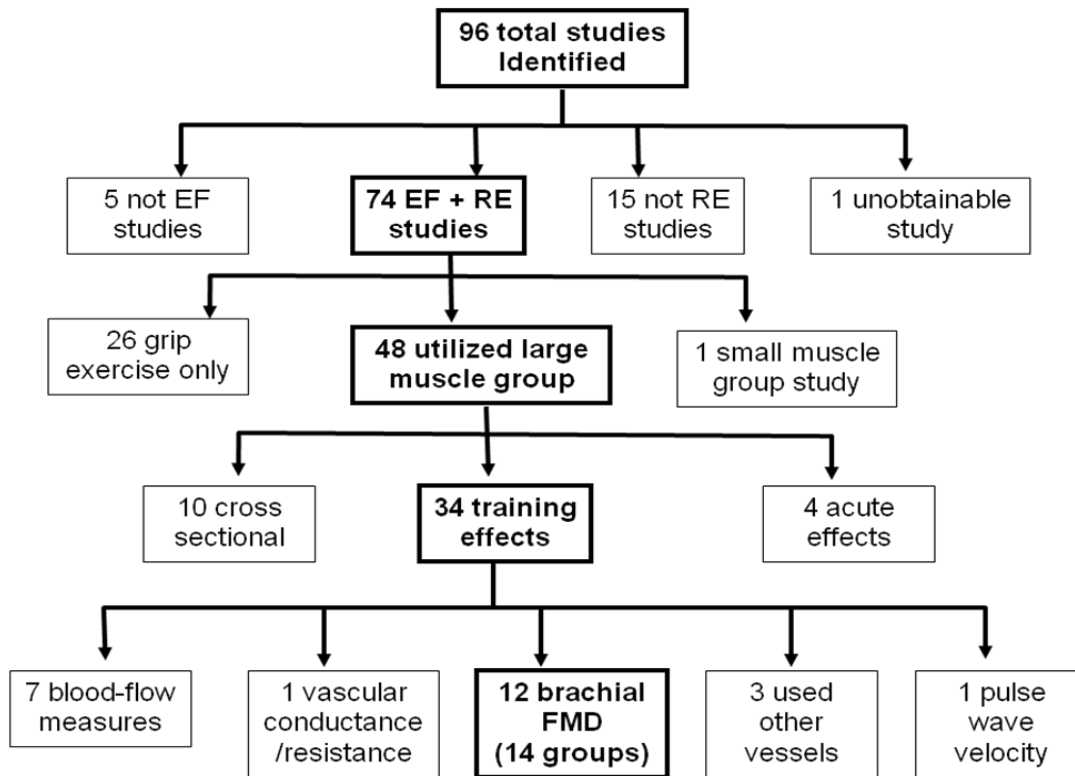


Figure 1- Study selection

$$SD_{\text{pooled}} = \sqrt{\frac{(N_E - 1)SD_E^2 + (N_C - 1)SD_C^2}{N_E + N_C - 2}}$$

Figure 2 - Equation for calculating  $SD_{\text{pooled}}$  from Coe, 2002

Table 1- Study group numbers and mean ages

RT Variable	groups reporting	mean N	sd	range
experimental subjects	14	23.0	17.2	11.0-75.0
control subjects	11	18.6	11.5	10.0-41.0
subjects' age	14	31.8	18.4	10.0-58.7



Table 2- Means of moderating variable of each group

Study	Exp N	Con N	Age (years)	Warm up	Aerobic included	Duration (weeks)	Frequency (days/wk)	N of exercises	N of sets	N of reps	Intensity (%1RM)	Set to failure	Interset rest (s)
Maiorana 2001	16		52	Y	Y	8	3	7	1	15	60	N	60
Olson 2006	15	15	38	Y	N	52	2	9	3	9		Y	
Woo 2004-1 year	22	41	10	Y	Y	52	2	9					
Okamoto 2007 RT/run	11	11	18.5	Y	Y	8	2	7	5	9	80	N	120
Walsh 2003 treated	11	11	52	Y	Y	8	3	7	1	15	60	N	60
Green 2003-2004	75	16	53.1	Y	Y	8	3	7	1	15	60		15
Clarkson 1999	25		18	Y	Y	10							
Woo 2004- 6 wk	41	41	10	Y	Y	6	2	9					
Casey 2007B	13	10	58.7	Y	N	18	2	10	1	12		Y	
Walsh 2003 untreated	11	11	53	Y	Y	8	3	7	1	15	60	N	60
Rakobowchuk 2005&A	28		28	N	N	12	5	6	3	8	80	Y	120
Watts 2004	19	20	14.3	Y	Y	8	3	7	1	15	63	N	75
Casey 2007	24	18	21	Y	N	12	3	7	2	10		Y	90
Okamoto 2007 run/RT	11	11	18.5	Y	Y	8	2	7	5	9	80	N	120

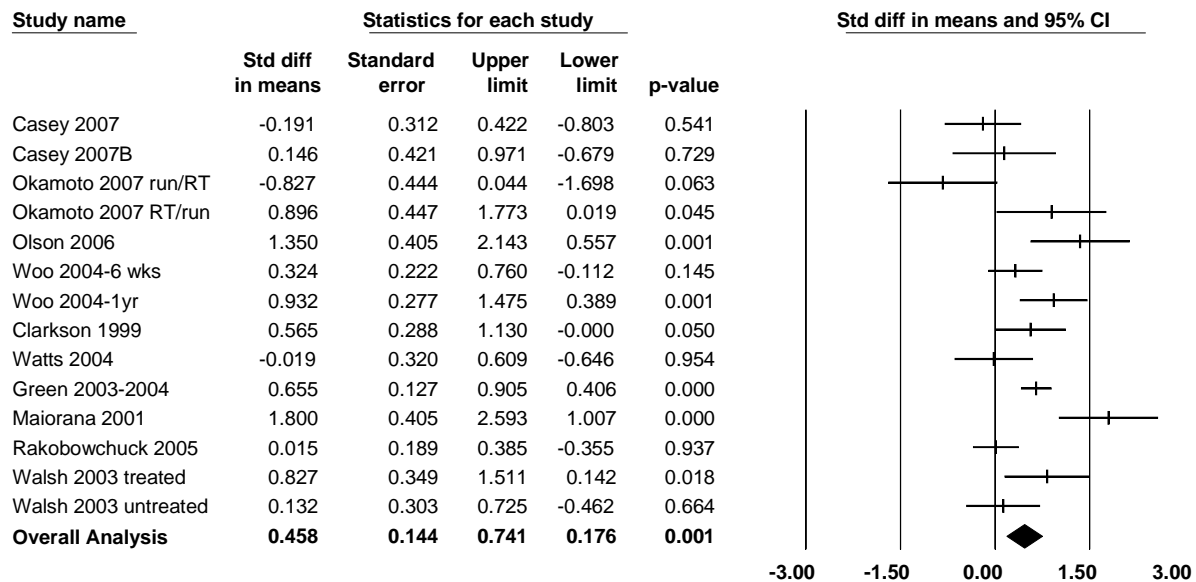


Figure 3 - Forest plot of standard difference in the means

Table 3- Summery of significant moderating variables

	Moderator Variables				Inter-set rest
	age	# sets	# reps	% 1RM	
Point estimate	0.0092	-0.1582	0.7576	-0.0318	-0.0067
SE	0.0038	0.0678	0.0265	0.0097	0.0019
Q	5.788	5.449	8.2	10.795	12.155
df	1	1	1	1	1
p-value	0.0161	0.02	0.004	0.001	0.0005

## Appendix- Studies included in analysis

1. Casey, Darren P., Darren T. Beck, Randy W. Braith. (2007). Progressive resistance training without volume increases does not alter arterial stiffness and aortic wave reflection. *Experimental Biological Medicine*. 232, 1228-1235.
2. Casey, Darren P. Gary L. Pierce, Kathy S. Howe, Mark C. Mering, Randy W. Braith. (2007). Effect of resistance training on arterial wave reflection and brachial artery reactivity in normotensive postmenopausal women. *European Journal of Applied Physiology*. 100, 403-408.
3. Clarkson, Peter, Hugh E. Montgomery, Michael J.U. Mullen, Ann E. Donald, Amanda J. Powe, Teresa Bull, Michael Jubb, Michale World, John E. Deanfield. (1999). Exercise training enhances endothelial function in young men. *Journal of the American College of Cardiology*. 33, 1379-1385.
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13. Woo, Kam S. Ping Chook, Chung W. Yu, Rita Y.T. Sung, Mu Qiao, Sophie S. F. Leung, Christopher W. D. Lam, Con Metreweli, David S. Celermajer. (2004). *Circulation*. 109, 1981-1986.

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## Evaluation of possible mechanisms of obesity-related changes in forearm blood flow: an acute resistance exercise model

### **Abstract**

Evaluation of Possible Mechanisms of Obesity-Related Reductions in Forearm Blood Flow: an Acute Resistance Exercise Model. **Introduction:** The time course of changes in forearm blood flow (FBF), adiponectin, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) are not well characterized following resistance exercise (RE) in obese and non-obese subjects. This study tested the hypothesis that an acute bout of RE would alter FBF, adiponectin, and TNF- $\alpha$ , that those changes would be greater in obese versus non-obese subjects, and that the changes in circulating cytokines would be related to changes in FBF. **Methods:** Subjects ( $n = 28$ ) were recruited and assigned to one of two groups: 1) those with body fat  $\leq 30\%$  (non-obese,  $N = 10$ ) and 2) those with body fat  $> 30\%$  (obese,  $N = 18$ ). All subjects completed a one repetition maximum (1RM) test protocol using leg flexion and leg extension exercises, and subsequently completed four sets of 8 repetitions at 85% of 1 RM. FBF, subjective muscle soreness, serum adiponectin, TNF- $\alpha$ , and creatine kinase (CK) were evaluated at baseline (rest), immediately post-RE, 1 hour post-RE and 24 hours post-RE. **Results:** Height, body mass, percent fat, fat mass, and BMI were significantly different ( $p < 0.05$ ) between the two groups. A 2 group x 4 time point repeated measures ANOVA revealed a significant interaction between the two groups ( $p = 0.004$ ). Contrasts revealed group differences in the direction of changes between

baseline and post-RE ( $p = 0.05$ ), post-RE and 24 hour post-RE ( $p = 0.003$ ) and 1 hour post-RE and 24 hours post-RE ( $p = 0.025$ ). Changes in FBF were not related to changes in adiponectin or TNF- $\alpha$ , however, when controlling for baseline cytokine levels, changes in TNF- $\alpha$  at 24 hours post- were negatively correlated to changes in adiponectin post-RE ( $r = -0.431$ ,  $p = 0.031$ ) and 24 hours post-RE ( $r = -0.397$ ,  $p = 0.05$ ). There were no overall or group differences in serum CK values; however, subjective soreness changed over time ( $p = 0.001$ ) with significant changes from baseline to post-RE ( $p = 0.009$ ), 1 hour post-RE ( $p = 0.001$ ), and 24 hour post-RE ( $p < 0.001$ ). **Discussion:** These results indicate that FBF measures in obese and non-obese react in a divergent pattern immediately following RE but return to baseline within 24 hours. These changes are not related to changes in adiponectin or TNF- $\alpha$ .

## Introduction

Measures of endothelial function have been shown to be predictive of cardiovascular events such as stroke and heart attack (Fichtlscherer, Breuer, & Zeiher, 2004). Endothelial dysfunction, or the reduced ability of an artery to dilate when subjected to shear stress, is thought to be one of the earliest clinical indicators of atherosclerosis. (Huang et al., 2007; Perticone et al., 2001). Several chronic disease states have been shown to affect the functioning of the endothelium including type 2 diabetes, insulin resistance, dyslipidemia, hypertension and obesity (Yki-Jarvinen, 2003; Brook, 2006; Govindarajan, 2008).

Of these chronic disease states, obesity is one of the fastest growing and is related to the development of the others. From 1962 to 2002, obesity ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ) among individuals over 20 years old in the United States increased from 13.3% to 30.4% of the

population while those overweight and obese (BMI > 25) increased from 44.8% to 65.1% (Wang, Wood, & Trayhurn, 2007). Furthermore, treatment of obesity represents 7% of global health expenditures (Stapleton, James, Goodwill, & Frisbee, 2008). In addition, obesity is associated with a variety of cardiovascular risk factors such as atherosclerosis, insulin resistance, type 2 diabetes, dyslipidemia, hypertension and endothelial dysfunction (Brook, 2006; Govindarajan, 2008). There are several mechanisms by which obesity can contribute to endothelial dysfunction, including activating the renin-angiotensin cascade, increasing sympathetic tone (Govindarajan, 2008), and contributing to leptin (Hickey & Calsbeek, 2001), and insulin resistance (Yki-Jarvinen, 2003).

Obesity has also been shown to result in the elevation of several pro-inflammatory cytokines, which are secreted by adipose tissue. These include C-reactive protein, IL-6, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Adiponectin, an anti-inflammatory cytokine, is found in lower levels in obese subjects (Fantuzzi, 2008). This low-grade inflammatory state can cause endothelial dysfunction subsequent to a reduced nitric oxide bioavailability, an increased attraction of adhesion molecules to the endothelial cell wall, and an increased infiltration of leukocytes which stimulate an increase in smooth muscle cells. Additionally, inflammation can increase thrombogenesis and fibrinolysis through increases in plasminogen activator inhibitor (Brevetti, Silvestro, Schiano & Chiariello, 2003). Increased adiponectin, however, can improve endothelial function as higher adiponectin increases insulin sensitivity, fatty acid uptake, and the bioavailability of nitric oxide (Chen, Montagnani, Funahashi, Shimomura, & Quon, 2003). Additionally, adiponectin has been shown to inhibit the pro-inflammatory effects of TNF- $\alpha$  as well as

its synthesis (Ye, Gao, Yin, & He, 2007; Kobashi et al., 2005; Matsuzawa, Funahashi, Kihara, & Shimomura, 2004).

Adiponectin works in mainly an endocrine manner but has functions that are also autocrine and paracrine. Adiponectin decreases insulin resistance as well as decreasing hepatic glucose production and increasing triglyceride breakdown in muscle and other tissue, helping to control blood glucose levels. It also causes an increased production of high-density lipoprotein in the liver which serves to reduce levels of low-density lipoproteins. In vessels, adiponectin reduces the expression of adhesion molecules on endothelial cells, increases the action of endothelial nitric oxide synthase and increasing bioavailability of NO. It also reduces systemic inflammation by inhibiting production of TNF- $\alpha$  and inhibiting its actions, in turn reducing production of C-reactive protein and interleukin-6 as well as inhibiting the functions of interleukin-2. These actions occur in macrophages, either in the vessels or in macrophage infiltrated inflammatory sections of adipose tissue (Simpson and Singh, 2008)

Resistance exercise (RE) is not universally regarded as beneficial to vascular functioning, with some training studies demonstrating improvements (Anton et al., 2006; Copeland et al., 1996; Watts et al., 2004; Woo et al., 2004) and others demonstrating reductions in endothelial function (Cortez-Cooper et al., 2005). Chronic RE training increases forearm blood flow (Maiorana et al., 2000; Selig et al., 2004) though there are concerns that it may have a negative effect on conduit artery function (Bertovic et al., 1999; Otsuki, 2006) due to the high blood pressures experienced during heavy resistance exercise (MacDougall, Tuxen, Sale, Moroz, & Sutton, 1985). The effects of acute resistance exercise on vascular function have received less attention in the scientific

literature. Improvements have been demonstrated in flow mediated dilation following a lower body resistance exercise bout but only in trained individuals and only immediately post-exercise (Varady, Bhutani, Church, & Phillips, 2009). Additionally, Varaday et al. (2010) demonstrated increases in adiponectin in resistance trained, non-obese subjects after RE. Other researchers have shown increases in adiponectin after RE training (Fatouros et al., 2005) while effects of RE on TNF- $\alpha$  however, are varied (Nieman et al., 2004; Tsai et al., 2006). Adiponectin and its effects on TNF- $\alpha$  may play a role in changes in vascular function after acute bouts of RE.

The purpose of this study was to examine the effects of an acute bout of RE on FBF, adiponectin and TNF- $\alpha$  in non-obese and obese individuals. It was hypothesized that an acute bout of RE would increase FBF, adiponectin and decrease TNF- $\alpha$  in both non-obese and obese subjects post-exercise, 1 hour post exercise and 24 hours post-exercise. Additionally, we hypothesized that the changes in inflammatory cytokines would correspond to the changes in FBF, that the changes would be greater in the non-obese compared to obese subjects, and that changes in adiponectin would be inversely related to changes in TNF- $\alpha$ .

## **Methods**

*Subjects.* Twenty-eight subjects between the ages of 18 and 39 years were recruited for the study through personal contacts and classroom visits. Individuals diagnosed with diabetes or high blood pressure, with any known form of cardiovascular disease, smokers or those taking medications that would potentially affect vascular function were excluded from the study. Subjects completed an informed consent, a medical history questionnaire



and physical activity readiness questionnaire (PAR-Q) prior to enrollment in the study.

All procedures were approved by the VCU Institutional Review Board.

*Procedures.* Subjects visited the Health and Human Performance Laboratory (HHPL) two times on consecutive days. Subjects reported to the HHPL each day following an overnight fast. Subjects were instructed to refrain from exercise for three days prior to the start and during the course of the study. Subjects were also instructed to refrain from alcohol and caffeine for 24 hours prior to testing and during the two days of testing. All testing sessions commenced between 6 and 8 AM to avoid diurnal variations. Prior to the two days of testing, subjects were given detailed information regarding the purpose and the time requirements of the study. On day one, subjects sat quietly for 30 minutes prior to assessing body composition, resting blood pressure, assessment of leg soreness, and assessment of vascular function. A 7.0 ml blood sample was obtained from an arm or hand vein. Following these measures (baseline), a one repetition maximal strength test on a knee flexion and a knee extension variable resistance machine was completed following previously published guidelines (Bachle & Earle, 2008). After a brief recovery period (one minute), subjects completed four sets of eight repetitions, or until failure, with 85% of one repetition maximum on each machine with one minute inter-set rests. Immediately following the exercise bout, measures of muscle soreness, blood pressure, vascular function, and a blood sample were again obtained and considered the immediate post-exercise values (post-RE). Subjects subsequently sat quietly for one hour following the completion of the exercise. Following one hour of quiet rest, soreness measures, resting blood pressure, vascular function measures and a blood sample was obtained (1 hour post-RE). On day two, following 30 minutes of quiet sitting, soreness measures,

resting blood pressure, vascular function measures and a blood sample were obtained.

This corresponded to 24 hours post-exercise (24 hours post-RE). Figure 1 displays the protocol timeline.

*Assessment of physical activity.* Subjects completed a one-week physical activity questionnaire (International Physical Activity Questionnaire (Ekelund et al., 2005).

Subjects were asked to recall, over the prior seven day period the number of days and average number of minutes per day they engaged in vigorous or moderate physical activity and walking activity as well as the number of minutes spent sitting per day.

Vigorous physical activity minutes were summed over the week and multiplied by 6 METS, while moderate activity and walking were multiplied by 4 METS and 3.3 METS respectively to calculate total MET minutes of each activity. The MET minutes for each activity were then summed for a total MET minutes per week. Days of activity were calculated by adding the number of days the subjects reported engaging in vigorous activity to the number of days they reported engaging in moderate physical activity.

Subjects were classified into low, moderate and high activity groups based on previously published criteria (Craig et al., 2003) and the IPAQ website, [www.IPAQ.ki.se](http://www.IPAQ.ki.se) to check for differences in levels of activity between groups (*Guidelines for data processing and analysis of the international physical activity questionnaire (IPAQ)*, 2005).

*Blood sampling.* A 7.0 ml blood sample was obtained from an antecubital or hand vein on the subject's left side if possible following endothelial function testing (performed on right arm). Blood was obtained after assessment of FBF in order to avoid any stress-related effects on the FBF measures. The blood sample was collected in serum separator tubes and allowed to clot for 30 minutes. It was then centrifuged at 10,000g for 15

minutes and the serum was then aliquoted into storage tubes and immediately frozen at -80°C until analysis.

*Anthropometric measures.* Height to the nearest 0.5 centimeter and mass to the nearest .25 kilogram were assessed with a wall-mounted stadiometer and digital scale, respectively. Body composition was assessed with bioelectrical impedance analysis (Quantum 10, RJL) on day 1. A total body analysis was performed for determination of percent body fat and percent fat free mass. Percent body fat was multiplied by mass to calculate fat mass and percent fat free mass was multiplied by mass to calculate fat free mass. BMI was calculated by dividing mass in kg by height in meters squared.

*Resistance Exercise Testing.* Each subject performed a one repetition maximum strength test of the knee extensors then knee flexors. Briefly, each subject was fitted to the appropriate variable resistance machine (Nautilus, USA) by adjusting the back support to position the knee in line with the machine's axis of rotation. The subject did not perform any warm up other than the incremental testing protocol to avoid any possible effects of the warm up on FBF. The weight stack was adjusted to a minimal resistance and the subject was asked to complete one repetition. One repetition is considered to be moving the knee from the beginning position to 170 degrees or more of extension on the knee extension machine and from the starting position to 90 degrees or less of flexion on the knee flexion machine. Upon successful completion of the movement, the subject reported the difficulty of the lift on a 1-10 scale and when the difficulty was reported to be a 7 or higher, the subject rested for one to two minutes. Then 2.27-9.1 kg (5-30 pounds) was added to the weight stack, depending upon feedback from the subject regarding the difficulty of the previous effort, and the movement attempted again. This

continued until the subject failed to complete a repetition at which time the previous successful repetition was considered the one repetition maximum for that movement.

The procedure was then repeated with knee flexion.

*Acute Bout of Resistance Exercise.* One minute following the completion of the second movement test, the resistance of the leg extension and knee flexion was adjusted to 85% of the one repetition maximum rounding up to the closest 2.27 kg (5 pound) setting. The subject completed four sets of eight repetitions, or until volitional failure with one minute inter-set rests of the knee extension then knee flexion.

*Assessment of vascular function.* Blood pressure was assessed in the left arm prior to blood flow measures. Forearm blood flow (FBF) was assessed using mercury in-Silastic strain-gauge plethysmography (MSGP; Model AI6, D.E. Hokanson, Inc., Bellevue, WA). To accomplish this, blood pressure cuffs were positioned around the subject's upper right arm and right wrist. A mercury in-Silastic strain gauge was placed around the forearm approximately 10 cm distal to the olecranon process (Alomari et al., 2004; Alomari & Welsch, 2007). During each trial, the wrist cuffs were inflated to a pressure of 250 mmHg to occlude hand circulation. Forearm blood flow was determined using an upper arm venous occluding pressure of 40mmHg for 10 seconds followed by a pressure of 0 mmHg for 10 seconds. This was repeated for 3 minutes for a total of nine measurements. Subsequently, the upper arm cuff was inflated to 250 mmHg to occlude forearm blood flow for a period of 5 minutes. After 5 minutes of occlusion, the cuff was released and blood flow measures were repeated during the period of post-ischemic reactive hyperemia.

All blood flow wave forms were analyzed by a single technician utilizing the peak of the first pulse waves following the end of venous occlusion unless artifact required using additional waves to determine average inflow in ml of blood per 100 ml of tissue. Area under the curve was determined by the trapezoidal method by first averaging each pair of measurements with the equation:  $AUC = [(X + Y)/2] \times 20$  where X and Y are two sequential 10 second blood flow measures and then summing the 9 averages to obtain a 3 minute total area under the curve (AUC). Pre-ischemic AUC forearm blood flow was taken as the average 10 second blood flow from the nine measures prior to the ischemic stress, peak blood flow was the highest 10 second average blood flow following the ischemic stress, usually the first or second 10 second period. Excess FBF (ExFBF) was calculated by subtracting pre-ischemic FBF AUC from the post-ischemic FBF AUC.

*Assessment of mechanical pain threshold.* Mechanical pain threshold was assessed on the front of the thigh, mid-way between the hip crease and proximal edge of the patella and midway between mid-thigh and the proximal edge of the patella. Pressure was applied with increasing force at a rate of approximately  $1 \text{ kg} \cdot \text{cm}^{-2} \cdot \text{second}^{-1}$  using a dial algometer (Effegi, Alfonsine, Italy) with a  $1.5 \text{ cm}^2$  application head until the subject reported a painful sensation or until the upper limit was reached. The upper limit of force applied was set at  $5 \text{ kg/cm}^2$  to avoid bruising. Each point was measured 3 times with a 10 second interval between trials. The mean of the second and third trials, if the subject reported any soreness, was used for analysis. Subjective pain perception was assessed during an active unweighted knee extension using a visual analog scale which was 100 mm in length with the left side of the scale marked “no soreness” and the right side marked “extreme soreness” (Hubscher, Vogt, Bernhorster, Rosenhagen, & Banzer, 2008).

Subjects were instructed to mark the line with a single vertical line at the point that represented how much pain or soreness they felt in the right upper leg during active extension. The distance from the left end of the line to the subject's mark was measured and recorded as a number 0-100.

*Analysis of blood samples.* Concentrations of adiponectin were determined by ELISA utilizing a commercially available kit (ALPCO, Salem, NH). TNF- $\alpha$  concentrations were determined using a high-sensitivity ELISA utilizing a commercially available kit (R and D Systems, Minneapolis, MN). Creatine Kinase concentrations were also determined utilizing a commercially available ELISA kit (Prolias, Rockville, MD). Standard curves were generated on each plate and all samples were run in duplicate. Intra assay coefficients of variation were 19.9 percent for CK, 8.1 percent for TNF- $\alpha$ , and 5.37 percent for adiponectin. A single technician performed all assays. Plate aspiration and washing was performed using an eight channel automated plate washer (Model 1575, Bio-Rad, Hercules, CA), absorbance was read using an automated microplate reader (Model 680X, Bio-Rad, Hercules, CA) and values were generated using a computer-based system (Microplate Manager, Bio-Rad, Hercules, CA).

*Data Analysis.* Subjects were divided into two groups, non-obese (body fat  $\leq$  30%) and obese (body fat  $>$  30%). Independent samples t-tests were utilized to test for differences between group demographic data and baseline measurements. Dependent variables were excess FBF area under the curve values (ExFBF), blood marker values, subjective soreness values, or the respective blood marker fraction values. Blood marker fraction values were calculated by dividing values of blood markers at post-RE, 1 hour post-RE, and 24 hours post-RE by values at baseline to control for differences in baseline values.

A two-way repeated measures ANOVA was performed with each dependent variable and group (non-obese versus obese) and time (baseline, post-RE, 1 hour post-RE, and 24 hours post-RE) as factors to reveal a main effect of group and/or time. If a significant interaction between group and time was present in any two-way repeated measures ANOVA, contrasts were used to determine the location of differences in the slopes of changes between time points. Additionally, a Tukey *post hoc* test was used to locate differences in values at particular time points. Additionally, Pearson product-moment correlations were utilized to evaluate relationships at baseline among forearm blood flow, adiponectin, TNF- $\alpha$ , and creatine kinase and activity levels and demographic data. Data were analyzed utilizing commercially available software (PSAW 18, SPSS Inc. Chicago, IL).

## **Results**

### *Baseline Measures*

*Anthropometric measures.* A total of 28 subjects (12 females, 16 males) completed the research protocol. The subjects were divided into an obese (obese; body fat > 30%; N=18) and a non-obese (non-obese; body fat  $\leq$ 30%; N=10) group. Height, weight, BMI, percent fat, and fat mass were significantly different between the two groups ( $p < 0.05$ ). There were no significant differences in demographic variables or in reported exercise volume between the groups. Baseline anthropometric, laboratory and physical activity participation data are presented in Table 1.

*Baseline cytokine concentrations.* Baseline adiponectin and TNF-  $\alpha$  values were not significantly different between groups. Baseline adiponectin was negatively correlated to body mass ( $r = -0.669$ ,  $p < 0.001$ ) BMI ( $r = -0.663$ ,  $p < .001$ ), percent fat ( $r = -0.388$ ,  $p =$

0.05), and fat mass ( $r = -0.590$ ,  $p = 0.002$ ). Baseline TNF- $\alpha$  was significantly correlated to body mass ( $r = 0.479$ ,  $p = 0.013$ ).

*Baseline FBF.* ExFBF was not significantly different between the two groups at baseline; however, the non-obese group had nominally higher ExFBF. Baseline ExFBF correlated to MET minutes of vigorous exercise ( $r = 0.520$ ,  $p = 0.006$ ), however, most subjects did not report any vigorous exercise in the previous week. When subjects reporting no vigorous physical activity were excluded from the analysis, the correlation was no longer significant ( $r = 0.744$ ,  $p = 0.09$ ), though the trend remained.

#### *Time Course of FBF, Cytokines, and Muscle Soreness*

*Time course changes in FBF.* Overall, there were no significant main effect for ExFBF area under the curve (ExFBF) across the 4 measurement time points ( $F(3,78) = 1.193$ ,  $p = 0.318$ ). However, there was a significant ExFBF group by time interaction ( $F(3,75) = 4.737$ ,  $p = 0.004$ ). Repeated measures contrasts found significant differences between groups in changes between baseline and post-RE ( $F(1,25) = 4.245$ ,  $p = 0.05$ ), post-RE and 24 hours post-RE ( $F(1,25) = 11.216$ ,  $p = 0.003$ ) and between 1 hour and 24 hours post-RE ( $F(1,25) = 5.682$ ,  $p = 0.025$ ). *Post hoc* analyses at each time point indicated a significant difference between groups at the 24 hour time point, where the ExFBF of the non-obese group was greater than the ExFBF of the obese group ( $t = 2.116$ ,  $p = 0.044$ ). Figure 2 presents the group by time changes in ExFBF. The interaction remained significant when controlling for baseline ExFBF values ( $F(2,50) = 5.504$ ,  $p = 0.007$ ).

*Adiponectin.* There were no significant main effect for adiponectin over time ( $F(1.991,43.802) = 2.53$ ,  $p = 0.091$ ) nor any group by time interaction ( $F(1.991,43.802) = 0.58$ ,  $p = 0.563$ ) (Figure 3).



*TNF- $\alpha$* . There were no significant main effect for TNF- $\alpha$  over time ( $F(1.907,41.954) = 0.708$ ,  $p = 0.492$ ) nor any interaction by group over time ( $F(1.907,41.954) = 1.048$ ,  $p = 0.357$ ). Inflammatory cytokines were not related to ExFBF at any time point. However, controlling for baseline cytokine levels, fraction values of TNF- $\alpha$  at 24 hours post-RE were negatively correlated to fraction values of adiponectin post-RE ( $r = -0.431$ ,  $p = 0.031$ ) and 24 hours post-RE ( $r = -0.397$ ,  $p = 0.05$ ) (Figure 3).

*Creatine Kinase*. Finally, there were no significant overall changes in CK over time ( $F(3,66) = 0.921$ ,  $p = 0.436$ ) nor was there any group by time interaction ( $F(3,66) = 0.591$ ,  $p = 0.623$ ) (Figure 4).

*Muscle Soreness*. There was no group by time interaction of subjective soreness ( $F(3,75) = 0.544$ ,  $p = 0.654$ ), however there was a significant main effect of muscle soreness over time ( $F(3,75) = 7.11$ ,  $p = 0.001$ ), indicating that all subjects reported more soreness after RE. Post-hoc analysis indicated that there was significantly greater muscle soreness reported at post-RE ( $p = 0.009$ ), 1 hour post-RE ( $p = 0.001$ ), and 24 hour post-RE ( $p < 0.001$ ) compared to baseline values (Figure 4).

## **Discussion**

This study tested the hypothesis that a bout of RE would increase forearm blood flow, that those changes would correspond to changes in the anti-inflammatory cytokine adiponectin and the pro-inflammatory cytokine TNF- $\alpha$ , and that those changes would be greater in non-obese versus obese subjects. ExFBF was different between groups only at 24 hours post-RE where the non-obese group had greater ExFBF. However, changes in ExFBF over time were different between the groups. The ExFBF of the obese group increased from baseline to post-RE while the non-obese experienced a decrease in

ExFBF, though neither change was significant within groups. The change in ExFBF was also different between groups from post-RE to 24 hours post-RE and from 1 hour post-RE to 24 hours post-RE; the non-obese group showed an increase in ExFBF to a level near baseline while the obese group showed a decrease in ExFBF to a level below baseline. Again, neither change was significant within groups (Figure 2). There were no significant changes in adiponectin or TNF- $\alpha$  and neither was related to ExFBF, however, both related to measures of adiposity. The change in TNF- $\alpha$  was negatively correlated to changes in adiponectin.

The current study found results immediately post exercise that were similar to previous studies (Bousquet-Santos, Soares, & Nobrega, 2005; Ferrara et al., 2006; Umpierre, Stein, Vieira, & Ribeiro, 2009) with the non-obese untrained group experiencing a decrease in ExFBF. The obese group, however, demonstrated a significantly different change in ExFBF. These data are also similar to previous studies in that ExFBF returned to baseline within one hour following exercise (Bousquet-Santos et al., 2005; Ferrara et al., 2006; Umpierre et al., 2009).

Varaday et al. (2010) and Fernandez et al. (2010) have demonstrated increases in flow mediated dilation immediately after lower body RE in lean, trained subjects, but not in lean untrained subjects. The current study also evaluated untrained, non-obese subjects and found similar results immediately post exercise. At 1 hour post-RE and 24 hours post-RE, ExFBF increased in the non-obese group and decreased in the obese group. This is most likely the result of the subjects returning to baseline following RE. Umpierre, et al. (2009) found no increases in endothelial function in healthy subjects 24

hours post exercise and these data agree with previous research, though at 24 hours post-RE, the non-obese group had a significantly higher ExFBF than the obese group.

The hypothesis of this study was that adiponectin and TNF- $\alpha$  levels would change due to RE and that those changes would relate to changes in ExFBF. However, there were no changes in either cytokine nor did concentrations of adiponectin and TNF- $\alpha$  relate to ExFBF. There are several alternative mechanisms, however, that may be responsible for the changes in ExFBF observed. Previous research had indicated that overweight/obese subjects have blunted vascular responses to acute endurance exercise (Harris, Padilla, Hanlon, Rink, & Wallace, 2008). Haram et al. (2006), however, found time course changes in endothelial function that were similar to our non-obese group in rats. The decreases in vasodilation directly post exercise in that study were prevented when vessels were incubated with superoxide dismutase, a free radical scavenger, indicating the presence of oxidative stress on the endothelium during and directly after exercise. Reactive oxygen species (ROS), also called free radicals, form during heavy exercise (Di Francescomarino, Sciartilli, Di Valerio, Di Baldassarre, & Gallina, 2009). ROS can interfere with nitric oxide availability and combine with it to form a reactive nitrogen species that inhibits nitric oxide synthase. While the current study did not measure ROS production, subjective measures of muscle soreness significantly increased over time and delayed onset muscle soreness has been linked to productions of free radicals during exercise (Armstrong, 1990; Close, Ashton, McArdle, & Maclaren, 2005) though the exact mechanism has yet to be elucidated. During high intensity RE, epinephrine and norepinephrine increase above baseline levels (W. Kraemer et al., 1999) and may also cause vasoconstriction as well as increased ROS (Di Francescomarino et

al., 2009; Stapleton et al., 2008). Increases in lactic acid/acidosis can also increase levels of free radicals (Finaud, Lac, & Filaire, 2006). A myogenic response to the acute increase in blood pressure following RE may generate ROS as well (Higashi & Yoshizumi, 2004). The non-obese subjects may have experienced a return to baseline because they are better able to cope with exercise-induced increases in free radicals due to higher anti-oxidant levels at baseline (Vincent, Innes, & Vincent, 2007). ROS typically return to baseline in lean untrained subjects after 24 hours (Rognmo et al., 2008) which would agree with the results of the current study. Lastly, increases in angiotensin II as levels has been shown to increase after a brief maximal bout of lower body RE (W. Kraemer et al., 1999).

The obese group, however, initially experienced an increase in ExFBF post-RE before reductions at 1 hour and 24 hours post exercise. Zhu, et al. (2010) found the repeated flow-mediated dilation (FMD) testing with ischemic stress caused increases in brachial artery dilation in obese subjects by itself within three repeated tests. No such effect of the testing itself was found in the lean group. Heffernan et al. achieved similar changes in peripheral PWV (Heffernan, Edwards, Rossow, Jae, & Fernhall, 2007) indicating a local effect. Prior research (Harris, Padilla, Rink, & Wallace, 2006) had shown no effects of repeated ischemic stresses, but only in lean subjects. Although the slight non-significant increase in FBF in the obese group in this study occurred in the second FBF trial, one cannot rule out the possibility that multiple tests had an intervention effect. Thus, several effects may have occurred during this protocol; 1) an increase in free radicals, angiotensin II and/or sympathetic nervous activity due to the strenuous exercise which decreased ExFBF in both groups and 2) a repeated ischemic

effect that could have been a strong stimulus to increase ExFBF, but only in the obese subjects.

*Changes in adiponectin.* At baseline, adiponectin levels were significantly lower in subjects with greater body mass, BMI, percent fat and fat mass. This result has been consistently demonstrated in previous studies as adiponectin, although synthesized by adipose cells, paradoxically, tends to be decreased in subjects with larger fat mass (Knudson, Dick & Tune, 2007). Results of studies evaluating the effect of exercise on adiponectin have been equivocal. A number of studies have demonstrated increases in adiponectin following resistance (Varady et al., 2010) and endurance exercise (Jurimae, Purge, & Jurimae, 2005; Jurimae et al., 2006); while others have not found an increase in adiponectin following endurance exercise (Jamurtas et al., 2006; R. Kraemer et al., 2003). Jamurtas et al. (2006) also measured adiponectin at 24 and 48 hours post-endurance exercise and found no change. Varady et al. (2010) found increases in adiponectin following RE, but only in subjects who were RE trained, not in runners or sedentary subjects. In the current study, no significant changes in adiponectin overall, or by group, over time were observed. Adiponectin may be more affected by changes in weight or fat mass than exercise (Esposito et al., 2003), in particular visceral fat, as removal of subcutaneous fat via liposuction does not consistently lead to increases in adiponectin (Esposito, Giugliano, Scuderi, & Giugliano, 2006). This relationship is evident in the correlations between measures of weight, fat mass, and baseline levels of adiponectin.

*Changes in TNF- $\alpha$ .* At baseline, TNF- $\alpha$  was positively correlated with body mass. This is in agreement with previous studies which show increased TNF- $\alpha$  with obesity (Bahceci et al., 2007). Endurance exercise and RE have been shown to alternately

increase levels of TNF- $\alpha$  (Ostrowski, Rohde, Asp, Schjerling, & Pedersen, 1999; Rahman, Abdullah, Singh, & Sosroseno, 2010; Nieman et al., 2004), reduce levels of TNF- $\alpha$  (Gokhale, Chandrashekara, & Vasanthakumar, 2007; Phillips et al., 2008; Tsai et al., 2006; Hirose et al., 2004; Phillips et al., 2008) or cause no changes (Ostrowski et al., 1998; Uchida et al., 2009). The current study did not show significant changes in TNF- $\alpha$ , though there was a tendency for increases in the obese group and no change at 24 hours in the lean group after a transient non-significant increase post-RE.

There is evidence that synthesis of TNF- $\alpha$  is inhibited by adiponectin (Knudson et al., 2007) and that the effects of TNF- $\alpha$  are suppressed by adiponectin (Kobashi et al., 2005; Matsuzawa et al., 2004; Devaraj, Torok, Dasu, Samols, & Jialal, 2008). In this study, fractional values of adiponectin at 24 hours post-RE negatively correlated to fractional values of TNF- $\alpha$  at 24 hours post-RE supporting the hypothesis that adiponectin inhibits TNF- $\alpha$  synthesis.

Adiponectin inhibits the production of TNF- $\alpha$  and TNF- $\alpha$  stimulation of NF- $\kappa$ B. Adiponectin inhibits the production of TNF- $\alpha$  through stimulation of the cyclic adenosine monophosphate- protein kinase A (cAMP-PKA) pathway and also stimulates the XI- $\kappa$ B pathway which inhibits TNF- $\alpha$  stimulated NF- $\kappa$ B (Kobashi et al., 2005). The findings here suggest that adiponectin does act in an autocrine or paracrine manner to inhibit production of TNF- $\alpha$ , however, no systemic increases in adiponectin suggest that its vascular-influencing endocrine effects, such as increased bioavailability of NO are not affected by RE.

*Soreness and CK.* Although subjects reported significantly greater muscle soreness compared to baseline, CK values did not increase over the 24 hour period.

Although this is unusual, it is similar to previous research (Nosaka, Newton, & Sacco, 2002) which found a significant increase in muscle soreness at 24 hours post-exercise, but significant changes in CK did not occur until measures made at 48 hours. Neither soreness nor CK correlated to any other variable. The increase in the soreness reported by the subjects would seem to suggest that the bout of RE was at least somewhat strenuous.

*Limitations.* The results of this study must be viewed within the context of several limitations. First, measures were only taken at three time points following exercise. Significant changes may have occurred at other time points that may have provided additional pertinent data related to the time course of changes in FBF following RE. The time points selected corresponded to typical published peaks of blood markers and ExFBF, however. Therefore, any selection of additional time points that might have given additional insight would be speculation. Also, the multiple measures of ExFBF utilizing ischemic stress may have acted as an intervention itself, obscuring the effects of the exercise bout. Secondly, subjects were recruited based on low or high BMI in order to generate low and high body fat percentage groups, however, a number of low BMI subjects had high percentages of body fat resulting in unequal group size. Measures of central adiposity, such as waist circumference and waist to hip ratio were not obtained. Considering the effects of visceral fat may be different than the effects of subcutaneous fat, these measures may have provided additional insight into the role of central adiposity in ExFBF, adiponectin and TNF- $\alpha$ . Thirdly, physical activity levels were determined using a survey (IPAQ) rather than more objective data such as accelerometry, leading to possible errors in recall by the subjects. Additionally, aerobic fitness was not measured

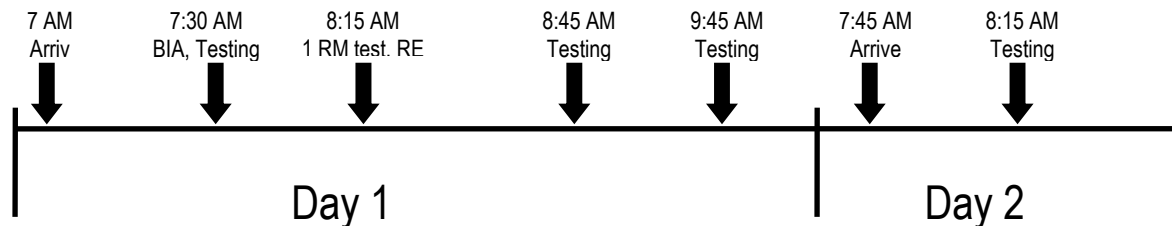
so the actual aerobic fitness of the subjects and its relationship to the results is unknown. Lastly, adiponectin and TNF-  $\alpha$  were the only cytokines measured in the study. The inclusion of additional vasoactive cytokines, such as leptin, resistin or endothelin-1 which may have provided further pertinent data related to the mechanisms altering ExFBF.

*Future studies.* Future studies should use a greater resistance exercise stress, more resembling a typical resistance exercise bout as promoted by the American College of Sports Medicine (American College of Sports Medicine, 2009), examine additional time points and cytokines, quantify aerobic fitness and compare the effects of fitness to total weekly activity. Additionally, trained obese subjects should be included to uncover the effects of obesity while accounting for training status. Finally, multiple measures of vascular function, including flow-mediated dilation, pulse wave velocity, and FBF should be used to determine if changes are systemic or if RE affects conduit and resistance arteries differently at different time points.

In summary, the divergent ExFBF results following RE between obese and non-obese subjects indicate that the effects of RE are variable in untrained subjects depending on adiposity with increases in obese subjects post-RE and decreases in non-obese subjects post-RE with a return to baseline within 24 hours. The variable effects may be due to the oxidative stress, changes in concentrations of vasoactive substances and/or repeated ischemic stresses. It does not appear to relate to changes in adiponectin or TNF-  $\alpha$  as there were no significant changes in cytokine concentrations and no significant relationship between those changes and ExFBF. The ability of obese trained individuals to cope with cardiovascular stress resulting from RE is unknown and the lack of data beyond immediately post RE for trained subjects makes speculation about the longer term



effects of acute RE difficult. Individuals who regularly participate in exercise may be better able to contend with increases in ROS, catecholamines and angiotensin II generated by exercise while sedentary obese subjects may be more susceptible to the negative effects of these vasoactive substances on ExFBF. Adiponectin and TNF-  $\alpha$  did not significantly change at the time points measured post-RE and did not significantly affect changes in ExFBF, though changes in TNF- $\alpha$  were negatively related to changes in adiponectin post-RE.



Testing includes: BP, pressure algometer, analog pain scale, FBF, blood draw

Figure 1- Timeline of testing

Table 1- Demographic and clinical characteristics of the study group

Variable	non-obese (n = 10)	obese (n = 18)	p- value
age (years)	26.3 $\pm$ 7.15	29.8 $\pm$ 6.75	0.212
females/males	3/7	9/9	0.206
height (cm)	176.9 $\pm$ 6.42	169.7 $\pm$ 9.76	0.046
weight (kg)	72.5 $\pm$ 16.90	95.3 $\pm$ 31.70	0.02
BMI (kg·m <sup>-2</sup> )	23.1 $\pm$ 4.51	32.9 $\pm$ 9.6	0.001
body fat (%)	23.6 $\pm$ 4.03	38.1 $\pm$ 7.64	<0.001
fat mass (kg)	17.4 $\pm$ 6.32	37.5 $\pm$ 17.25	<0.001
fat free mass (kg)	55.1 $\pm$ 11.25	57.8 $\pm$ 17.87	0.666
MET minutes per week	845.4 $\pm$ 576.63	2059.4 $\pm$ 499.48	0.282
exercise days per week	4.8 $\pm$ 2.05	4.1 $\pm$ 2.84	0.509
MET minutes of vigorous exercise	111.1 $\pm$ 185.23	127.1 $\pm$ 318.82	0.892
MET minutes of moderate exercise	317.8 $\pm$ 531.46	511.8 $\pm$ 979.52	0.588
MET minutes of walking	416.5 $\pm$ 337.40	798.9 $\pm$ 1271.89	0.258
minutes spent sitting	366.0 $\pm$ 107.52	476.3 $\pm$ 204.60	0.073
baseline adiponectin (μg/ml)	5.75 $\pm$ 2.096	5.64 $\pm$ 2.305	0.909
baseline TNF-α (pg/ml)	0.730 $\pm$ 0.4049	1.012 $\pm$ 0.4844	0.486

Values expressed as means and standard deviations

BMI-body mass index, MET-metabolic equivalent, TNF-α-tumor necrosis factor-α

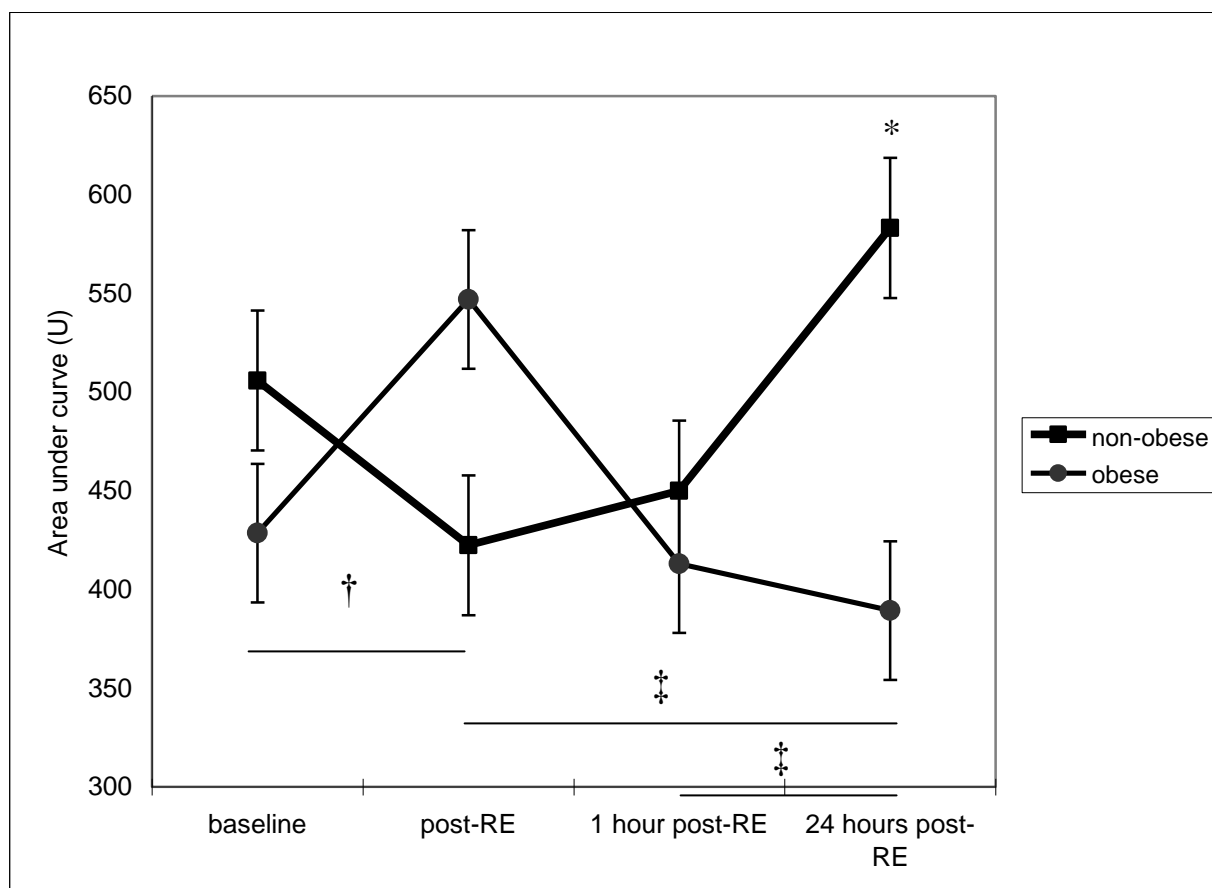


Figure 2- Relationship of changes in FBFAUC over time between groups

\* groups significantly different. †change significantly different between groups from baseline to post-RE. ‡ change significantly different between groups from post-RE to 24 hours post RE and from 1 hour post-RE to 24 hours post.  $\alpha = 0.05$ .

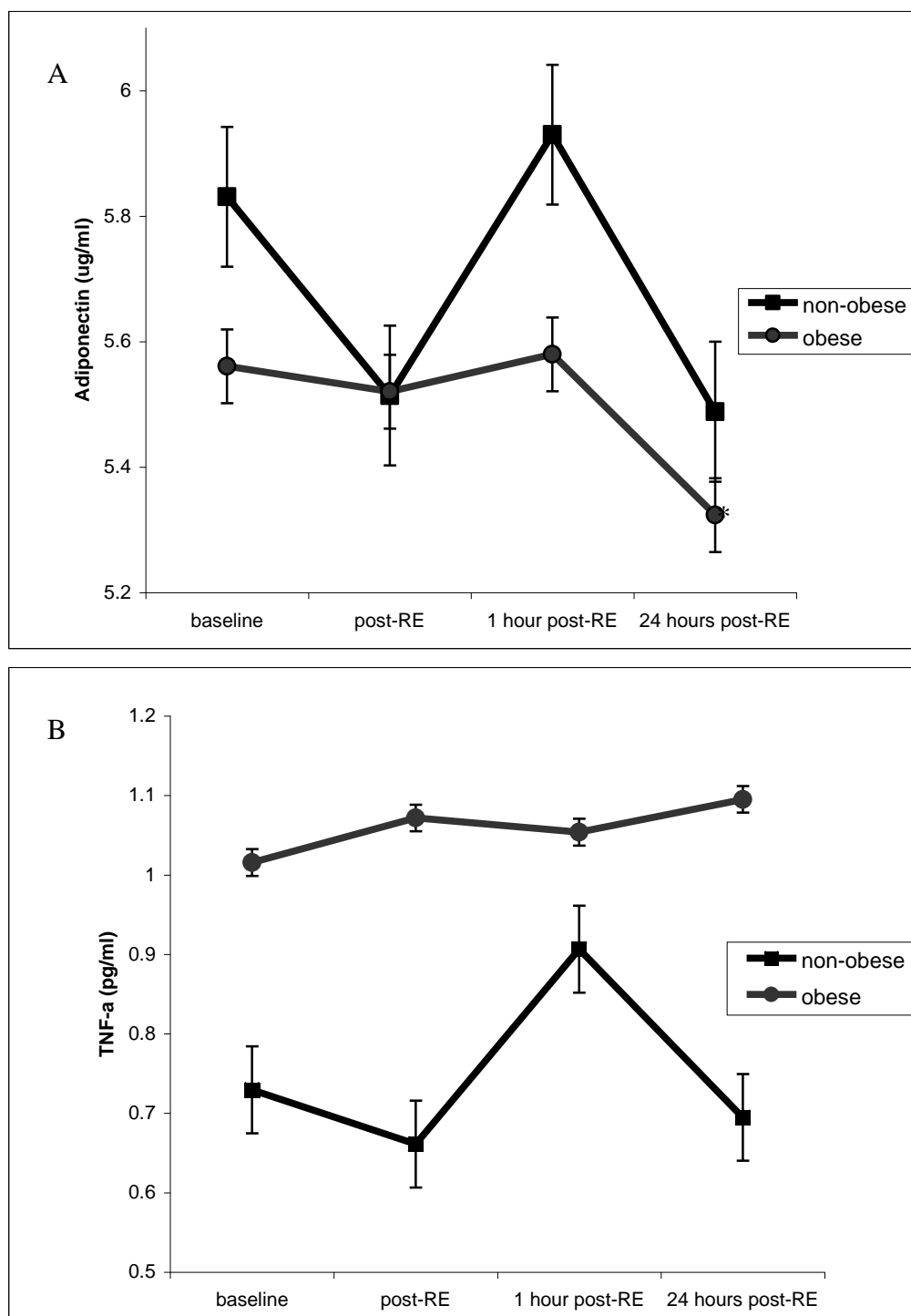


Figure 3- Relationship of changes in adiponectin (A) and TNF- $\alpha$  (B) over time between groups

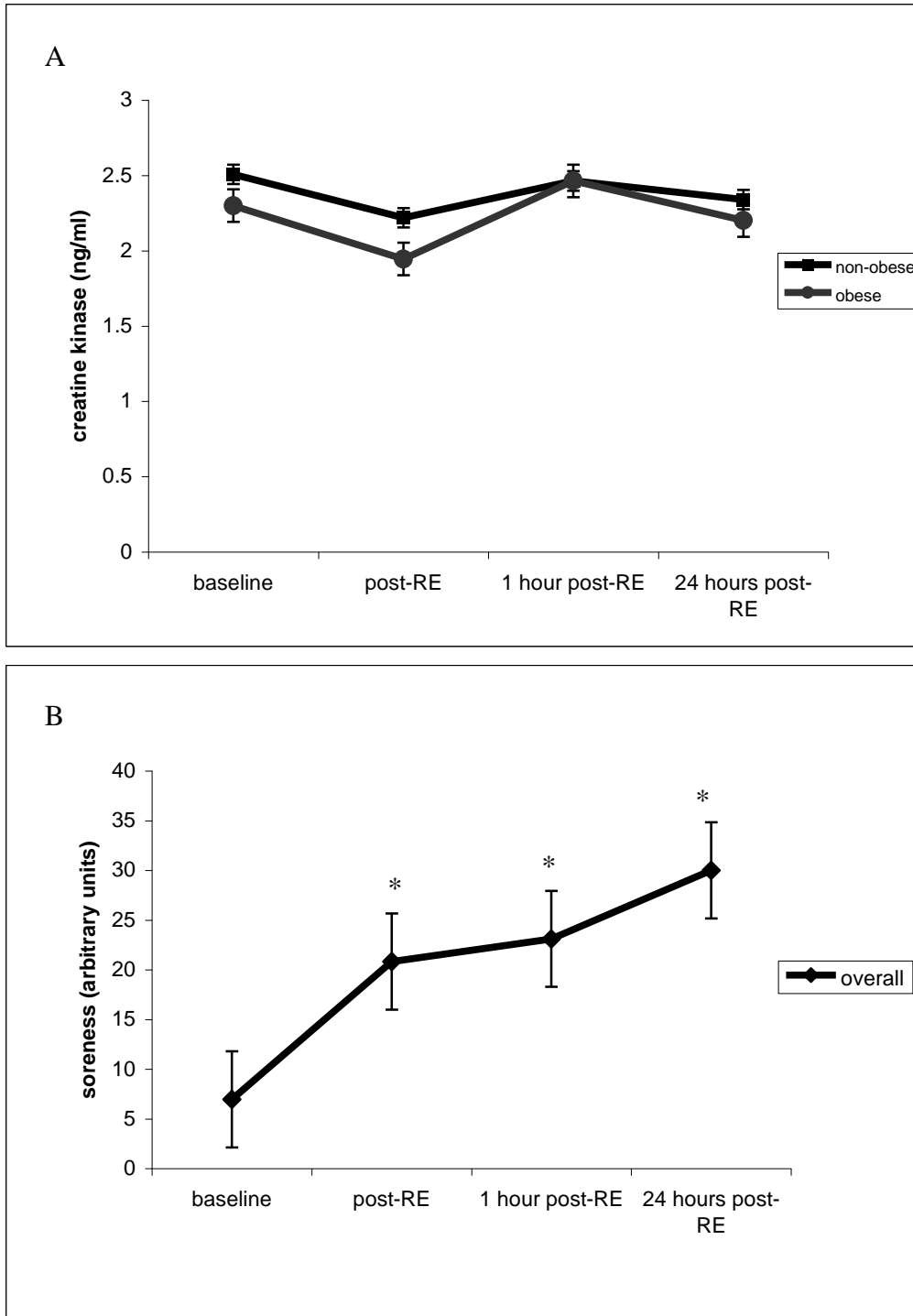


Figure 4- Relationship of changes in CK (A) and soreness (B) over time between groups  
\* significantly different from baseline  $\alpha = 0.05$

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## List of References

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## **Appendix A) Adiponectin ELISA procedures**

ALPCO Diagnostics, Salem, NH

Wash buffer was first reconstituted from 10X to 1X by adding 900 ml distilled water. Calibrator was diluted by adding 10 uL calibrator at 484.8 ng/ml to 1000 uL dilution buffer to form a 4.8 ng/ml solution. Then a serial dilution was created by taking 150 uL of the calibrator solution and adding it to 150 uL of dilution buffer in a serial manner to form calibrators in concentrations of 2.4, 1.2, 0.6, 0.3, 0.15 and 0.075 ng/ml. Dilution buffer alone was used as a 0 ng/ml calibrator.

Serum samples were first pretreated by adding 10 uL of the serum to 100 uL of buffer solution and 400 uL of sample pre-treatment buffer to form a 1: 51 dilution. Then, 10 uL of the pre-treated sample was added to 1.0 mL of dilution buffer to form a 1:5151 final sample dilution.

The plate was opened and 50 uL of calibrator dilutions or samples were added to the plate in duplicate. The plate was covered and allowed to incubate at room temperature for 60 minutes.

The plate was then aspirated and washed three times with 400 uL of the wash buffer with a 30 second soak prior to final aspiration using an automated plate washer (Model 1575, Bio-Rad, Hercules, CA) . The plate was then struck sharply onto paper towels 12 times to remove residual liquid.

Next 50 uL of biotin labeled-MoAb was added to each well with a multi-channel pipet. The plate was covered and allowed to incubate at room temperature for 60 minutes.

After incubation, the plate was washed again in an identical manner, then 50 uL of enzyme-labeled streptavidin was added to each well. The plate was covered and allowed to incubate at room temperature for 60 minutes.

After incubation, the plate was washed again. Lyophilized substrate was combined with 6 mL of substrate buffer in the substrate vial and 50 uL of the substrate solution was added to each well. The plate was covered and allowed to incubate for 10 minutes. Then, 50 uL of stop solution was added to each well.

The plate was read by an automatic plate reader (Model 680X, Bio-Rad, Hercules, CA) and plate reading software (Microplate Manager, Bio-Rad, Hercules, CA) was used to calculate a standard curve and unknown concentrations. The plate was read immediately at a wavelength of 490 nm optical density (after consultation with ALPCO technicians assured that the results would be valid as instructions called for 492 nm) and then corrected at 650 nm to account for distortion caused by the plate itself. The absorbance of the 0 ng/ml calibrator was subtracted from all other wells to calculate the change in absorbance. A linear curve was constructed using the calibrators and the unknown dilutions were plotted on to the curve to estimate actual concentrations. The calculated concentrations were then multiplied by 5151 to calculate serum concentrations of adiponectin.

## **Appendix B) TNF- $\alpha$ ELISA procedures**

R and D Systems, Minneapolis, MN

Wash buffer was first reconstituted from 10X to 1X by adding 900 ml distilled water. Lyophilized substrate was reconstituted with 6.0 mL of substrate diluent and mixed well. Lyophilized Amplifier was reconstituted with 6.0 mL of amplifier diluent and mixed well. TNF- $\alpha$  standard was reconstituted with 4.2 mL of calibrator diluent to produce a solution of 32 pg/mL concentration and was mixed gently for 15 minutes. A serial dilution was then created by adding 500 uL of the calibrator to 500 uL of calibrator diluent to form concentrations of 16, 8, 4, 2, 1, and 0.5 pg/mL. Calibrator diluent alone was used for a 0 pg/ml concentration standard.

First 50 uL of assay diluent was added to each well using a multi-channel pipet after mixing. Then 200 uL of standards or samples were added to each well. All analysis were completed in duplicate. The plate was covered and allowed to incubate at room temperature for three hours.

The plate was then aspirated then washed by adding 400 uL of wash buffer to each well using an automated plate washer (Model 1575, Bio-Rad, Hercules, CA) with a 2 minute soak. This was repeated a total of six times. The plate was then struck smartly on paper towels 12 times to remove any remaining liquid.

Next, 200  $\mu$ L of TNF- $\alpha$  HS conjugate was added to each well after mixing. The plate was covered and allowed to incubate at room temperature for 2 hours. The plate was then washed again as before.

Then, 50  $\mu$ L of substrate solution was added to each well, the plate covered and allowed to incubate at room temperature for 60 minutes. Without washing, 50  $\mu$ L of amplifier solution was added to the wells and covered. After 30 minutes of incubation at room temperature, 50  $\mu$ L of stop solution was added and the plate was immediately read by an automatic plate reader (Model 680X, Bio-Rad, Hercules, CA) and plate reading software (Microplate Manager, Bio-Rad, Hercules, CA) was used to calculate a standard curve and unknown concentrations. The plate was read immediately at a wavelength of 490 nm optical density and then corrected at 650 nm to account for distortion caused by the plate itself. The absorbance of the 0 ng/ml calibrator was subtracted from all other wells to calculate the change in absorbance. A linear curve was constructed using the calibrators and the unknown dilutions were plotted on to the curve to estimate actual concentrations.

## **Appendix C) Creatine Kinase ELISA procedures**

Prolias, Rockville, MD

First, 20 uL of standards or serums was added to each well in duplicate. Standards were in concentrations of 200, 100, 50, 15, 7.5, and 0 ng/mL and were ready for use. Next, 200 uL of enzyme conjugate reagent was added to each well and the plate was shaken at 45 rpm for 30 seconds to insure mixing. The plate was allowed to incubate for 60 minutes at room temperature before aspiration and washing with an automated plate washer (Model 1575, Bio-Rad, Hercules, CA) using 350 ml distilled water for a total of five washes. The plate was then struck onto paper towels to assure complete removal of liquid. Then, 100 uL of TMB reagent was added to each well and the plate was shaken again for 15 seconds and allowed to incubate for 20 minutes at room temperature. A 100 uL volume of stop solution was added to each well and the plate shaken for 30 seconds. The plate was immediately read at 450 nm optical density using an automatic plate reader (Model 680X, Bio-Rad, Hercules, CA) and plate reading software (Microplate Manager, Bio-Rad, Hercules, CA). The absorbance of the 0 ng/ml calibrator was subtracted from all other wells to calculate the change in absorbance. A linear curve was constructed using the calibrators and the unknown dilutions were plotted on to the curve to estimate actual concentrations. The upper two concentrations were eliminated as they were far beyond the concentrations of the unknown samples to create a better linear curve.



## **Appendix D) One repetition testing protocol**

1. Warm up w/light resistance for an easy 5-10 reps
2. 1 min rest
3. Estimate load that allows 3-5 reps by adding
  - +5-10% upper body
  - +10-20% lower body
1. 2 min rest
2. Estimate near-max load that allows 2-3 reps by adding
  - +5-10% upper body
  - +10-20% lower body
6. 2-4 min rest
7. Load increase by adding
  - +5-10% upper body
  - +10-20% lower body
6. Attempt 1RM
7. If successful, 2-4 min rest and repeat step 7
8. If unsuccessful, rest 2-4 min and decrease load by subtracting
  - 2.5-5% upper body
  - 5-10% lower body

(Baechle and Earle, 2000)

## **VITA**

Grayson Frederick Lipford was born May 4, 1972, in Portsmouth, Virginia, and is an American citizen. He graduated from Western Branch High School in Chesapeake, Virginia in 1990. He received his Bachelor of Science in Physical Education from the Longwood College in Farmville, Virginia in 1994. He received his Masters of Science in Kinesiology from the James Madison University in Harrisonburg, Virginia in 1997. He was certified as a Strength and Conditioning Specialist in the National Strength and Conditioning Association in 1997. Grayson Lipford was employed as a personal trainer and subsequently as fitness director and athletic director of the Richmond Athletic Club from 1997-2003. He was then employed as the wellness director at the Chester Branch of the YMCA of Greater Richmond then as the branch director of the James Center Branch of the YMCA of Greater Richmond from 2003-2006.